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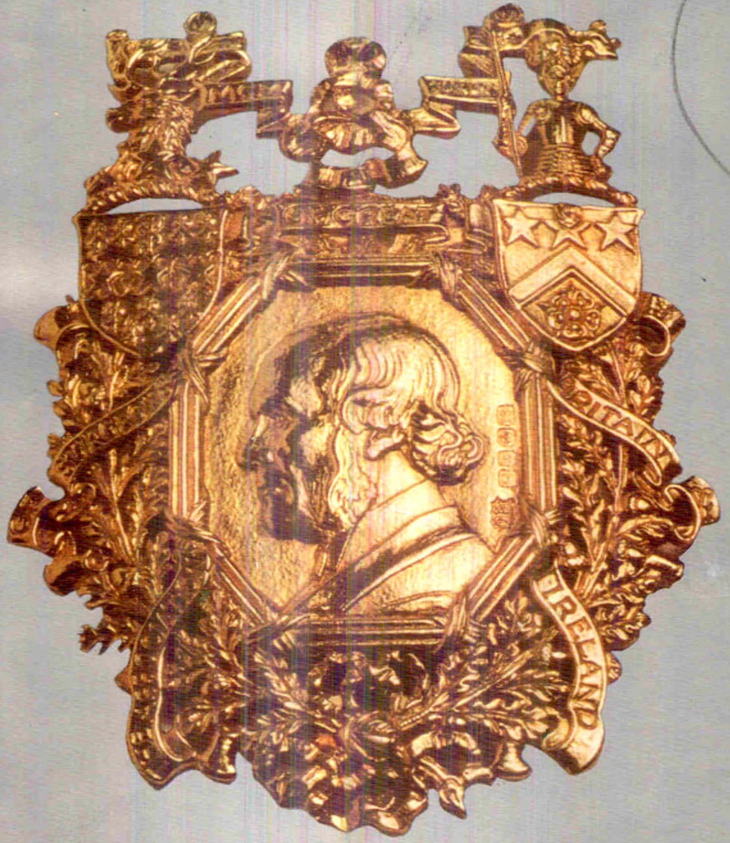

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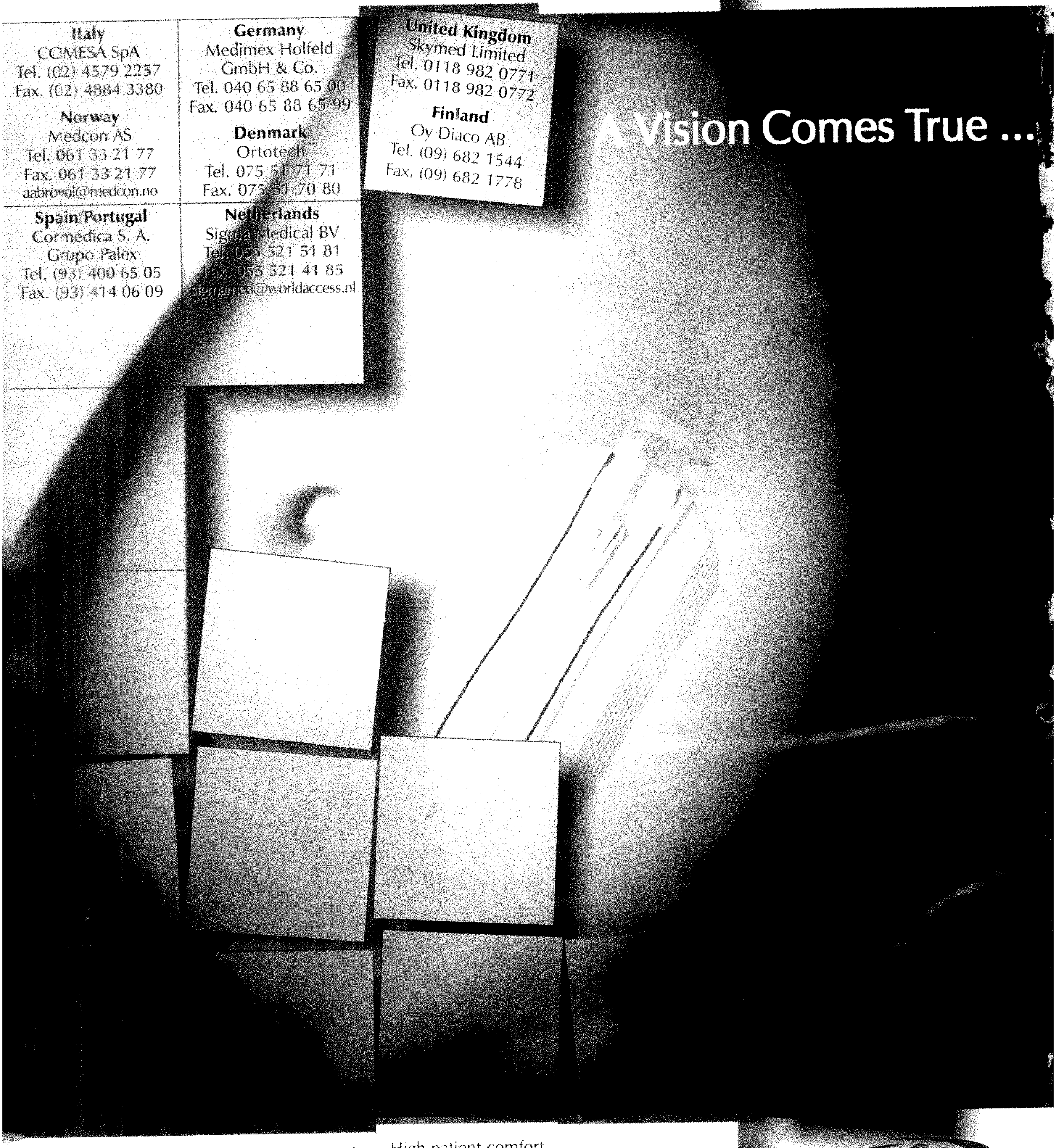

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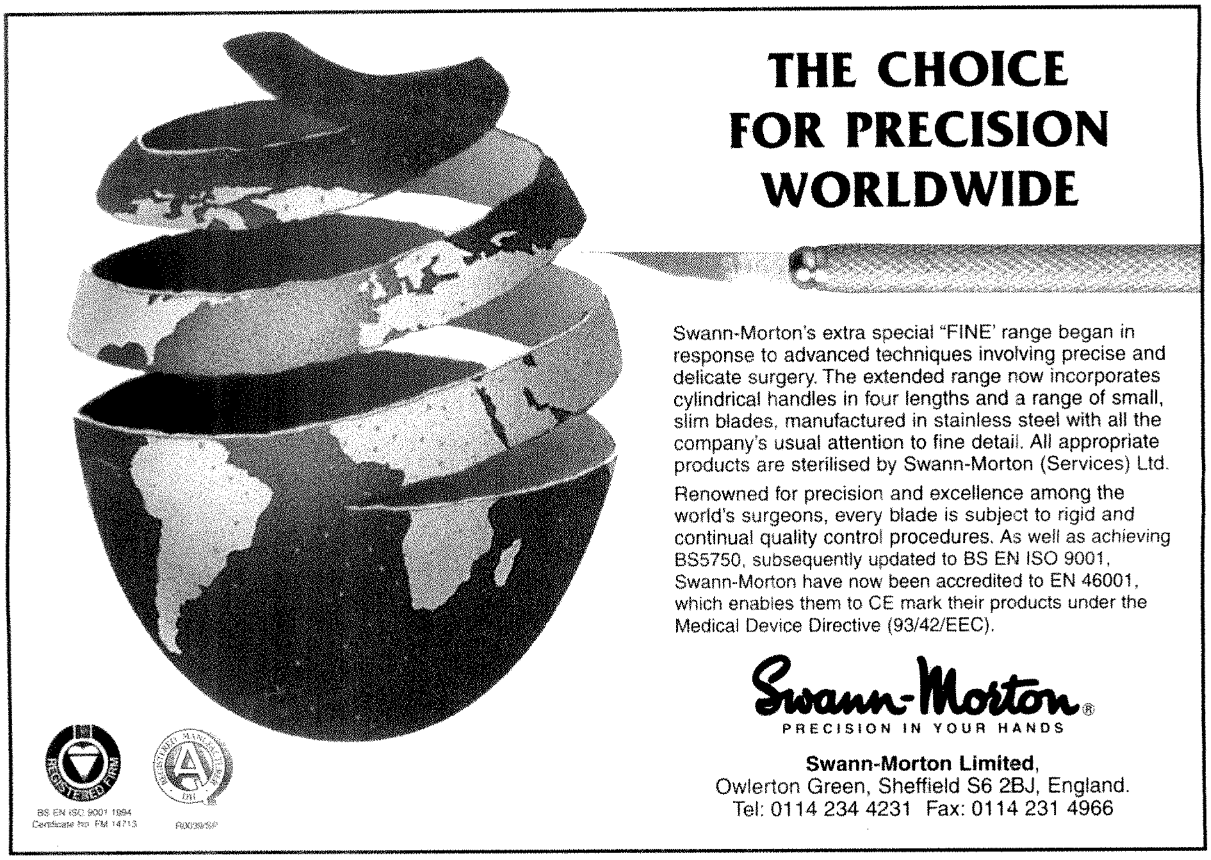

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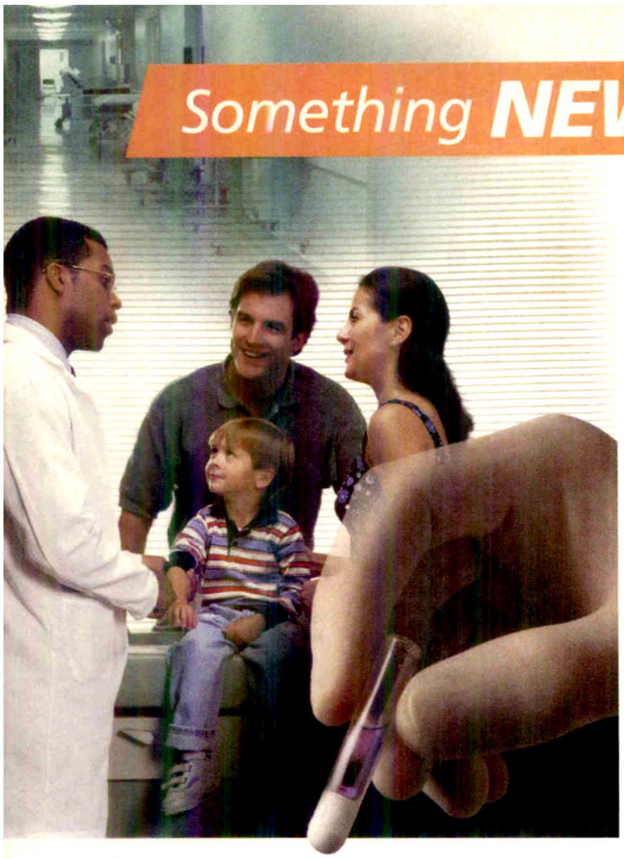

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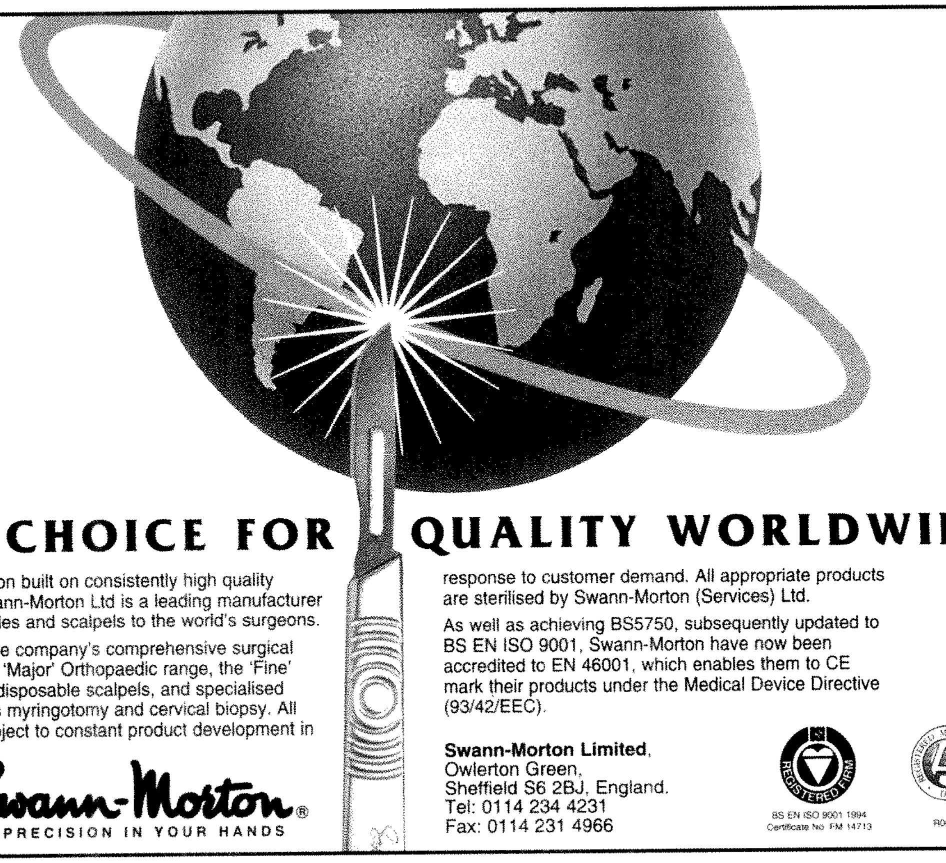

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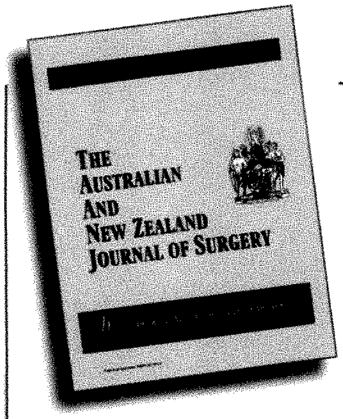

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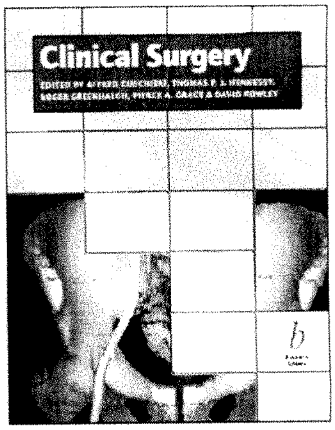

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Leading articles

Cancer surgery: why some survival benefits may be artefactual

Variations in the technique, or more often the extent, of cancer operations are frequently accompanied by reports of improvement in survival rate. Such improvement may, however, be an illusion and the force at play mere artefact. Common examples of such artefacts occur in the interpretation of results from selected case series, in the use of invalid comparison, and in situations where the stage-migration phenomenon might supervene.

Horton[1] believes that case series are the weakest evidence in assessing treatment efficacy, with uncontrolled bias and confounding as potentially lethal flaws. He also notes that case series comprise nearly half the articles in a recent group of leading surgical journals. Case series (and their treacherous terrain of retrospective audit) are frequently suspect, not only because of the possibility of uncontrolled bias but also because the information may be incomplete. In the absence of the rigour of planned pro formas and prospective data collection, adverse events and deaths may be missed or censored by innocent exclusion. On the other hand, formal trial entry with prospective pro formas yields sobering morbidity and mortality rates, particularly when dedicated data handlers collect the information. The greater operative morbidity and inferior survival rates found in prospective randomized trials, compared with those of single-centre (or single-surgeon) case series and retrospective audits, attest to this.

Invalid comparisons of disparate patient groups or disease stages may yield major cancer survival differences by artefact. One example is the comparison of the present with the past: the latest cohort (who underwent the newest intervention) almost invariably have the better result when compared with the previous cohort. The greatest caution must be used in interpreting such a comparison as, from a scientific viewpoint, the populations compared are completely unstable. The new cohort may be a group of particular interest to the chief investigator, whereas the previous one was managed by various surgeons in different wards or hospitals, and in different ways. The new intervention may also exhibit a 'halo' effect, which results in better and (particularly) special care for the select group. Thus, the improved survival may not be attributed to the operation in question, but to a multiplicity of other factors.

Clinical and intraoperative selection bias, with subsequent invalid comparison, has also artefactually improved survival rates in cancer surgery. This usually occurs when easily and safely resectable cancers are treated by the *big operation*, and those posing technical problems by the *small operation*. Here, however, it is the prior probability of the disease and its stage which are the real survival determinants, and not the big or small surgery. While stage-for-stage comparisons stabilize this to some extent, within each stage pigeon-hole there is an important range of disease extent, which might be enough to allow selection bias in type of surgery. Degrees of serosal invasion or adjacent organ infiltration (within the same stage) are examples of this. The big operation can only be compared with the small operation within the controlled environment of a randomized trial, where selection bias is largely removed. The 40 years of randomized comparisons of types of surgery for breast cancer is a good example of removal of bias, with a subsequent paradigm shift in thinking about surgery for cancer at this site.

The stage migration phenomenon refers to the artefactual improvement of survival results by more extensive staging[2]. Feinstein *et al.* found that their most recent cohort of patients with lung cancer fared significantly better, in each of the tumour node metastasis (TNM) stages, than a cohort treated in the 1960s; when, however, the most recent cohort was staged as the earlier cohort had been, without the benefit of ultrasonography, computed tomography and radionuclide scanning, all differences evaporated. The improved survival results were merely an artefact of better staging. Patients in the lower stages with clinically occult disease (usually nodal) were identified, extracted and placed in more advanced stage groupings (stage migration). The lower stages were thus 'cleansed' and survival rates improved admirably. The higher stages also benefited, as they received an addition of patients with low tumour burden. Thus, while each individual prognosis remained the same, as did that of the whole group, there was an apparent improvement for each of the individual stages.

The stage migration phenomenon is a serious artefact when radical is compared with less radical surgery. Radical surgery generally produces excellent survival results in case series and in unrandomized comparisons. The radical surgery usually consists of extensive lymphadenectomy, or dissections in the mediastinum, retroperitoneum or pelvis. Extensive and accurate staging is thus achieved, the stage groupings cleansed of patients with occult disease, and outstanding survival results are obtained. A possible example of this is reflected in the contemporary debate surrounding lymphadenectomy for gastric cancer, a debate which may also expand to include the radical resection of rectal cancer.

Patients who have radical lymphadenectomy for gastric cancer may appear to have superior survival rates than those managed more conventionally. Curiously, this survival advantage is also found in node-negative cases. In the ensuing debate all agree that the differences are due to the lymphadenectomy; the question is *how* lymphadenectomy achieves this. When submitted to the test of randomized trials, however, there seems to be no significant survival advantage to lymphadenectomy; not only this, but a higher morbidity rate is found in radically treated groups[3-5]. One argument is that an artefact is at play, probably the stage migration phenomenon. The Netherlands Triallists have gone further, hypothetically comparing, first, the staging in their patients as if there were a nodal yield from only conservative (D_1) dissection and, second, as if there were a radical (D_2) nodal yield[6]. As many as 30 per cent of patients are upgraded to a higher (N_2) nodal status, as well as further migration to N_3 or N_4 status, the result being artefactual and hypothetical improvement in survival.

Most major journals, including this one, have a heightened vigilance for the above artefacts. Many editors routinely refer proferred articles for statistical review. When cancer survival rates after surgery are reported or compared in future, a great deal more detail and scientific accuracy should be required. Randomized comparison, although an incomplete paragon[7], appears to be the robust test for new variations in the surgical treatment of cancer.

D. M. Dent

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Review

Endoluminal abdominal aortic aneurysm surgery

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Background The development of devices designed for the endoluminal repair of abdominal aortic aneurysm has led to the emergence of new endovascular techniques.

Methods Articles and case reports obtained from a Medline search of the English language literature from 1989 to 1997 are reviewed. This search was carried out using the MeSH heading 'aortic aneurysm, abdominal' and the keywords 'endovascular' and 'endoluminal'.

Results Reported mortality and complication rates for endoluminal aneurysm repair are similar to those following conventional repair, with the exception of continued perfusion of the aneurysm sac which remains a major problem following endoluminal repair.

Conclusion Successful endoluminal aneurysm exclusion is associated with reduced aneurysm diameter. However, longer term results of endoluminal repair, in particular of sealed endoleaks, are required before randomized controlled trials of endoluminal *versus* conventional repair can be undertaken.

In the 46 years since the first successful replacement of an abdominal aortic aneurysm (AAA) with a homograft was reported in 1952[1], the technique of open surgical repair of AAA has been refined to the extent that the elective operative mortality rate is now about 5 per cent[2,3], while the mortality rate from ruptured AAA remains about 50 per cent[2]. These figures apply only to selected patients, however; the risks of surgical repair are greater in those with significant co-morbidity[4]. As many patients with AAA have co-existent conditions that significantly increase the risk of both elective and emergency surgery[4], less invasive endovascular techniques of repair that reduce this risk may offer a means of reducing morbidity and mortality rates following operation. This paper describes the current status of endovascular AAA repair in clinical practice. It reviews the published results of endoluminal repair in series in which outcome measures and complications have been reported.

Development of endoluminal surgery

Percutaneous treatment of occlusive arterial disease has become an increasingly accepted part of vascular surgical practice since 1969 when Dotter first reported the percutaneous placement of stainless steel coils within the arterial lumen[5]. Percutaneous angioplasty and arterial stenting are now routine. These endovascular techniques are believed to offer advantages in terms of reduced morbidity and mortality rates, reduced hospital stay, and shorter convalescence, with results that are often similar to those of surgical treatment[6].

Although initially confined to occlusive disease, endovascular techniques have now been adapted for aneurysmal disease. Animal studies indicated that it was feasible to undertake endoluminal repair of aortic aneurysms with home-made stent–graft combinations introduced using a percutaneous catheter technique[7]. The first endoluminal repair of AAA in humans was reported in 1991[8,9]. The early endoluminal devices implanted in humans were all improvised[7,8,10,11], generally using commercially available stents and graft materials[12–14]. While there are no randomized studies to support the belief that endovascular techniques offer advantages in terms of reduced morbidity and mortality rates, endovascular AAA repair is associated with less postoperative respiratory dysfunction and reduced analgesic requirements[15]. While such endoluminal repair is minimally invasive, it is not a true percutaneous technique, as it requires either iliac or femoral artery dissection and arteriotomy[10–14,16].

Since the initial report[8], the feasibility of endovascular aneurysm repair in selected patients has been clearly established and a number of commercially prepared devices are currently undergoing clinical evaluation; long-term results are still awaited. Early reports suggested that, in high-risk patients, the procedure is associated with a significant mortality rate[16]. A number of procedure-specific postoperative complications have also been identified[17–19]. As a result, a number of authors have expressed reservations about the suitability of the technique for the majority of aneurysms[20,21], and attempts are now being made to ensure that both the devices implanted and the operative procedures employed are subjected to appropriate scientific scrutiny[22–24]. At the present time, critical appraisal of the results of endoluminal AAA repair is hampered by the absence of universally adopted reporting standards[23], and by the diversity of techniques and devices used. However, in view of the potential advantages that endoluminal repair offers over conventional AAA surgery[25], it is likely that it will continue to be developed and refined.

Principles of endoluminal grafting

Endoluminal AAA repair uses minimally invasive techniques to exclude the aneurysm sac from the arterial

Paper accepted 12 January 1998

circulation by fixing a prosthetic graft within the aortic lumen. Until recently, the absence of any commercially available device resulted in the repair being performed with a wide variety of different 'home-made' devices[8–14,26–29]. Most of these consisted of some combination of tubular or bifurcated graft material fixed in position with metallic stents or other mechanism to anchor the graft material to non-dilated arterial wall above and below the aneurysm. Some of these improvised devices are now either available commercially or undergoing commercial evaluation[10,11,30]. Other devices have been developed primarily in the commercial sector[18,31].

There are three principal means of excluding an AAA from arterial blood flow (*Fig. 1*) and most devices fall into one of three design categories (*Table 1*). Within these categories there is some variation in the method of attaching the device within the aortic lumen; some favour the use of anchoring stents with unsupported graft fabric between these stents[16,30], some use a custom-designed device to attach the graft throughout its length[10], and some of the most commonly used devices consist of metallic stents covered in fabric[31,32].

Aneurysm morphology

The suitability of an aortic aneurysm for endoluminal repair depends predominantly on aneurysm morphology and device design. With current devices there is a requirement for a proximal neck of at least 15 mm of normal aorta below the renal arteries to enable proximal anchoring without the device encroaching on the renal ostia. With most reported systems the aortic neck must have a maximum diameter[33] of 26 mm, although some delivery systems may accommodate grafts suitable for use in vessels up to 30 mm in diameter[34]. In addition, the iliac vessels must be of sufficient diameter to enable the passage of the introducing device into the aorta (at least 7–9 mm in diameter). Disadvantageous morphological features are listed in *Table 2*, although increasing experience with endoluminal surgery has led to many becoming only relative contraindications. The adjunctive technical manoeuvres required to overcome some of these contraindications have been well documented[35]; in some cases devices have even been deployed with the proximal uncovered portion of the stent lying across the renal ostia, without adverse effect[13,16,30].

Initial reports suggested that between 4 and 14 per cent of patients with AAA would be suitable for endoluminal repair using an aortoaortic tube graft[19,36–38]. With the recent availability of bifurcated and aortouni-iliac devices, and increasing experience with endoluminal techniques, some authors now report that up to 50 per cent of AAAs may be suitable for endoluminal repair[33,38,39]. These figures need to be interpreted with caution, however, as there remains considerable debate about the need to operate on small aneurysms[20,40], particularly in the absence of any reliable data on aneurysm expansion rates[41]. Furthermore, endoluminal surgery is currently being carried out in tertiary referral centres with highly selected patient populations; this is hardly representative of the generality of aneurysm management.

Radiological imaging and endoluminal surgery

In contrast to open repair, where the vascular surgeon can adapt both graft and anastomoses to the aneurysm morphology[20], endoluminal repair requires that the graft device is of the correct diameter, length and configuration at the time of deployment. Precise preoperative measurements are therefore needed[38,42]. These are best obtained by biplanar angiography with a calibrated catheter to correct parallax and magnification errors[42,43].

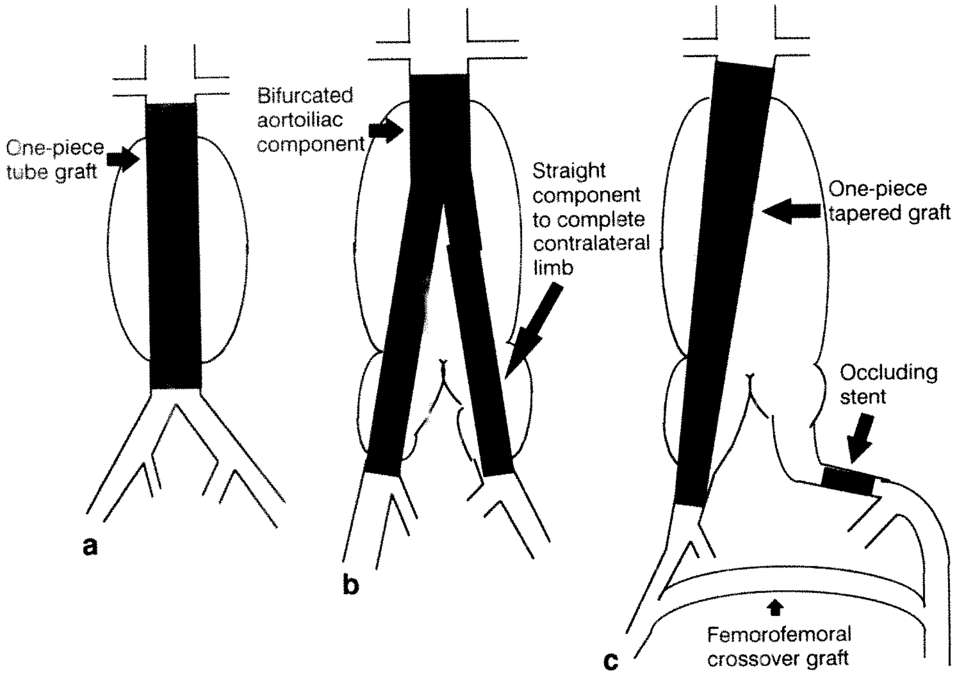
One-piece tube graft
a
Bifurcated aortoiliac component
Straight component to complete contralateral limb
b
One-piece tapered graft
Occluding stent
Femorofemoral crossover graft
c

Fig. 1 Diagrammatic representation of the three main categories of endoluminal repair of abdominal aortic aneurysm. a Aortoaortic tube graft; b aortobi-iliac graft; c aortouni-iliac graft with occlusion of contralateral iliac artery and femorofemoral crossover graft

Table 1 Three main categories of device currently being implanted for endoluminal repair of abdominal aortic aneurysm

Device type	Subgroups	Availability
Aortoaortic	Graft with proximal and distal stent or other attachment device	EVT (Endovascular Technologies, Menlo Park, California, USA) Parodi device*
	Externally covered stent	Passager (Boston Scientific, Oakland, New Jersey, USA)
	Internally covered stent	Corvita[32] (Corvita, Miami, Florida, USA)
	Modular graft with attachment device along graft length	Sydney endograft (Baxter Healthcare, Irvine, California, USA)
Bifurcated aortoiliac graft	Graft with proximal and distal stent or other attachment device	EVT Chuter–Gianturco*
	Externally covered modular stents	Vanguard (Boston Scientific) Talent (World Medical, Florida, USA) Perth bifurcated system*
	Internally covered stents	Corvita
	Modular graft with attachment device along graft length	Sydney endograft
Aortouni-iliac graft (and femorofemoral crossover)	Graft with proximal and distal stent or other attachment device	EVT Ivancev–Malmo system* Parodi device* Leicester device*
	Modular graft with attachment device along graft length	Sydney endograft

*Not currently available as commercially produced devices. All other devices are either undergoing clinical evaluation or are commercially available in some countries

Angiography in the assessment of AAA for endoluminal repair has limitations[43,44] and additional imaging is required[23]. Most centres use contrast-enhanced computed tomography (CT)[30,34,45], preferably with spiral acquisition and three-dimensional reconstruction[18,39,46]. Some authors advocate undertaking CT as the initial imaging procedure to determine suitability for endoluminal repair before angiography[18,34]. Future developments in preoperative imaging are likely to include the application of magnetic resonance imaging techniques[30,46–48].

Intraoperative monitoring and assessment of graft deployment are currently carried out using fluoroscopy[42,49], although some authors advocate the additional use of intravascular ultrasonography to determine graft length and site of deployment[42,50]. At present there are significant limitations to the routine use of intravascular ultrasonography[51], although it may have a role where mural thrombus or vessel wall irregularity is present at the site of graft anchoring. In these conditions angiography alone cannot confirm that the endoluminal device is accurately anchored to the aortic wall, rather than embedded in intraluminal thrombus, and interrogation of proximal and distal ends of the graft using intravascular ultrasonography can confirm appropriate apposition between the anchoring device and the vessel wall[41,51].

Table 2 Morphological features that do not favour endoluminal repair of abdominal aortic aneurysm

Involvement of renal artery origins*
Infrarenal proximal aortic neck length < 15 mm*
Proximal aortic diameter > 26 mm*
Common iliac artery diameter < 9 mm*
Common iliac artery < 25 mm long
Common and external iliac diameter > 14 mm
Distal aortic cuff < 10 mm (for aortoaortic tube grafts)
Thrombus within lumen at aortic neck
Angulation of iliac arteries > 90°
Angulation of proximal aortic neck > 60°

*Absolute contraindications with currently available devices; other features are relative contraindications

Mortality rate following endoluminal aortic aneurysm repair

Most of the published results indicate that the perioperative mortality rate following endoluminal AAA repair is similar to that reported for open repair (*Table 3*). The experimental nature of the technique has meant that many of the early devices were implanted in high-risk groups of patients who had often been refused the conventional operation[16,28,55,57]. While the reasons for this refusal are not always documented, 32 per cent of patients undergoing endoluminal repair in one large series were classed as American Society of Anesthesiologists grade IV[39]. In some series a small number of devices were inserted on an emergency basis for leaking aneurysms or contained ruptures[28,45,57]. When these factors are considered, in conjunction with the 'home-made' nature of the initial devices and the fact that the reported results include the initial 'learning curve' cases, it seems reassuring that the mortality rate associated with endoluminal repair is similar to that of conventional surgery.

Results of endoluminal aneurysm surgery

The technical success rate for endoluminal repair, defined as proper placement of the graft using endoluminal techniques without perigraft endoleakage, death or graft occlusion within 30 days of implantation[23], ranges from 48 to 95 per cent depending on the device deployed (*Table 3*). This is much lower than the success rate of conventional surgery which is in excess of 93 per cent[3]. Many endoluminal procedures require the placement of additional stents and devices to complete the exclusion of the aneurysm sac and to correct leaks noted at the time of initial device deployment[19]. These cases are not classed as primary technical successes[23]. Small leaks often seal spontaneously[39,53,57]. Correction of major leaks is usually attempted at the time of initial surgery or in the early postoperative period[19,39,55], in the same way that a vascular surgeon will insert additional sutures at an anastomosis to correct leaks observed when the clamps are removed during an open AAA repair. If these cases that are salvaged successfully with an additional endoluminal method are included, the success rate for the procedure reaches 100 per cent for some graft configurations (*Table 3*).

The mean hospital stay following successful endoluminal repair ranges from 3 to 12 days[39,42,45], with up to 72 per cent of patients discharged within 3 days of surgery in one series[53]. A number of authors have noted that with increasing experience they have been able to reduce the length of stay by 50 per cent[39,45].

The mean duration of operation reported for endoluminal procedures is 88–193 min, with an overall range of 25–480 min[28,39,42,45,53]. Some currently available devices are associated with a significant incidence of device-related problems that adversely affect the operating time, although not affecting outcome measures[58]. With more experience of endoluminal techniques, and improved devices and delivery systems, it is likely that these problems will be overcome. Operating times should, therefore, decrease and few patients will be subjected to prolonged endoluminal procedures[20].

Current reports of endoluminal AAA repair suggest that many of the aneurysms treated met recognized criteria for open surgical intervention[20]. All series report mean diameters between 51 and 60 mm, with AAAs as small as 36 mm and as large as 97 mm undergoing successful endoluminal surgery[39,54]. It is probable that smaller aneurysms are morphologically more suited to endoluminal repair[42] and the relevance of treating aneurysms of this size is debatable[20,40]; the favourable results associated with endoluminal repair may reflect a selection bias towards smaller lesions.

Table 3 Reported results of endoluminal repair of abdominal aortic aneurysm

Reference	Year	Device	*n*	Primary technical success	Success after additional endoluminal procedure	Conversion to open repair	Persisting endoleak or other late failure	Other postoperative complications	30-day mortality
Blum *et al.*[39]	1997	Aortoaortic	21	18 (86)	21 (100)	0	(6)	15 (10)	1 (1)
		Aortobi-iliac (Vanguard or Passager)	133	116 (87)	128 (96) [3]*	3			
Parodi *et al.*[16,42]	1995, 1997	Aortoaortic	51	81 (74)	93 (85) [2]*	4	16 (15)	8 (7)	5 (5)
		Aortouni-iliac	46						
		Aortobi-iliac (Parodi device)	12						
Chuter *et al.*[30,52]	1997	Aortobi-iliac (Chuter–Gianturco)	54	43 (80)	n.a.	3	14 (26)	n.a.	3 (6)
Moore and Rutherford[53]	1996	Aortoaortic (EVT)	46	22 (48)	32 (70) [9]*	7	7 (15)	27 complications (rate not stated)	0 (0)
Balm *et al.*[54]	1996	Aortoaortic (EVT)	31	24 (77)	27 (87) [3]*	1	3 (10)	34 complications in 23 patients	1 (3)
Yusuf *et al.*[28]	1997	Aortouni-iliac (Ivancev–Malmo)	30	25 (83)	25 (83)	5	3 (10)	6 (20)	2 (7) 3 (10) in hospital
Lawrence-Brown *et al.*[13]	1996	Aortobi-iliac (Perth device)	21	17 (81)	n.a.	0	7 (33)	11 (52)	1 (5)
White *et al.*[45]	1997	Aortoaortic	36	29 (81)	32 (89) [1]*	2	6 (8)	(33)	3 (4)
		Aortouni-iliac	20	19 (95)	19 (95)	1	0		
		Aortobi-iliac (White–Yu GAD)	20	15 (75)	15 (75)	5†	0		
May *et al.*[55,56]	1996, 1997	Aortoaortic	54	106 (88)	n.a.	15	n.a.	(15)	6 (5)
		Aortouni-iliac	26						
		Aortobi-iliac (GAD[41] and others)	41						
Marin *et al.*[57]	1995	All types (EVT and Parodi)	18	16 (89)	n.a.	n.a.	0 (0)	8 (44)	5 (28)
Thompson *et al.*[14]	1997	Aortouni-iliac (Leicester device)	25	20 (80)	n.a.	5	n.a.	6 (24)	2 (8)

Values in parentheses are percentages. Primary success refers to primary technical success rate as defined in the SVS/ISCVS (Society for Vascular Surgery/International Society for Cardiovascular Surgery) reporting standards[23]. *Totals include cases in which spontaneous thrombosis of endoleaks occurred (number in square brackets) within 6 months of surgery (primary clinical success[23]). †Includes one failed deployment treated by axillofemoral grafting. n.a., Data not available; GAD, graft attachment device

Early complications

The high complication rate following endoluminal repair includes complications that are exclusive to endoluminal surgery. There appears to be a specific 'postimplantation syndrome'[39] which takes the form of a spontaneously resolving pyrexia of unknown origin; it is of variable incidence and has not been reported by all authors (*Table 4*). The obligatory use of large-diameter delivery systems often results in injury to common femoral or iliac arteries, while the groin wound complication rate reflects the requirement for surgical exposure of these vessels (*Table 4*). Renal impairment following endoluminal repair may be secondary to the administration of large quantities of intravenous contrast agent[56]. Complications that are common to both endoluminal and conventional repair seem to occur with a similar incidence regardless of method[59,60].

Embolic events have been reported after endoluminal repair and in two centres these were fatal[14,42]. While this is a cause for concern, the overall incidence of peripheral embolic events following endoluminal surgery is less than that described for conventional repair[59].

Endoleaks

Endoleak is defined as the persistence of blood flow outside the graft lumen but within the aneurysm sac or adjacent vessels in which the graft is deployed[19,61]. It is a complication exclusive to endoluminal aneurysm repair. Endoleak that occurs at initial deployment may be due to a number of factors[62] and often arises at the site of proximal or distal fixation of the device. In selected cases further endovascular intervention to repair such primary endoleakage may be successful[19,39,42,62]. Trauma to the device fabric at the time of implantation has also resulted in both early and late endoleak[39,63]. Some early postoperative endoleakage appears to seal spontaneously (*Table 3*), although the long-term outcome of such sealed endoleaks is unknown[62] and they have been reported to recur[19]. Endoleakage can occasionally be identified using colour duplex ultrasonography to identify flow within the sac[19], but contrast-enhanced CT is the favoured method of follow-up[63] (*Fig. 2*) and has become the imaging modality of choice. If an endoleak is suspected, further investigation should be carried out using angiography.

Late complications

Although long-term follow-up of endoluminal AAA repair is not available, some late complications have already been observed. A small number of graft limb thromboses occurred early in the clinical development of a few bifurcated devices, but these have now been modified in an attempt to prevent further problems[13,30]. While these particular cases were related to early technical problems, late graft limb thrombosis may occur with endoluminal devices in the same way that it may occur in conventionally placed grafts[3]. Graft infection has also

Table 4 Complications reported following endoluminal repair of abdominal aortic aneurysm

Complication	Blum[39] (*n* = 154)	Parodi[42] (*n* = 109)	Moore[53] (*n* = 46)	Balm[54] (*n* = 31)	Yusuf[28] (*n* = 30)	Lawrence-Brown[13] (*n* = 21)	May[55] (*n* = 121)	Thompson[14] (*n* = 25)	Total (*n* = 537)
Local vascular complications									
Arterial access injury requiring surgery	3	1	8	6	—	—	9	—	27 (5)
Persisting endoleaks	2	10	1	2	3	4	3	—	25 (5)
Late-onset endoleaks	7	6	7	—	—	—	5	—	25 (5)
Wound or minor graft infection	—	—	6	1	—	1	6	2	16 (3)
Thromboembolic events leading to surgery	4	—	—	1	—	3	4	1	13 (2)
Minor embolic events	1	3	2	2	1	—	—	—	9 (2)
Blood loss requiring >2 units transfusion	—	—	—	6	—	—	1	—	7 (1)
Fatal embolic events	—	4	—	—	—	—	—	1	5 (1)
Lymph leak	2	—	1	1	—	—	—	—	4 (1)
Haematoma requiring surgical treatment	1	—	—	—	—	—	1	—	2
Arteriovenous fistula	1	—	—	—	—	—	—	—	1
Colonic ischaemia	—	—	—	—	1	—	—	—	1
Bowel perforation	—	—	—	—	—	—	—	1	1
Remote systemic complications									
Pyrexia	87	—	9	5	—	—	—	—	101 (19)
Renal failure	2	—	—	2	—	—	7	1	12 (2)
Myocardial infarct, cardiac failure or arrhythmia	—	—	—	2	1	1	8	—	12 (2)
Cerebrovascular event	—	—	—	1	1	1	3	—	6 (1)
Pneumonia	—	—	—	1	2	1	—	—	4 (1)
Respiratory failure	—	—	—	2	—	—	—	1	3 (1)
Hepatic or multiorgan failure	1	—	—	1	—	—	—	—	2

Values in parentheses are percentages. Only series in which individual complications are specified have been included. Complications are categorized according to the SVS/ISCVS (Society for Vascular Surgery/International Society for Cardiovascular Surgery) reporting standards for infrarenal aortic aneurysm repair[23] been reported as a late complication of endoluminal surgery[14,30], although the only bacteriologically confirmed case of infection arose in the femorofemoral crossover component of an aortouni-iliac graft[14]; there have so far been no confirmed reports of infected endoluminal devices themselves. Most late complications can be attributed to the development of endoleaks (*Table 5*). Persisting collateral flow into the excluded aneurysm sac from patent lumbar or inferior mesenteric vessels may result in late endoleak[39,63], although this appears to be a rare complication[19] and it is not routine practice to occlude these vessels before endoluminal repair of AAA. Some authors believe that the presence of intraluminal thrombus protects against endoleakage, but this remains to be confirmed.

Late endoleaks more commonly occur as a consequence of failure of the proximal or distal attachment device to remain in close apposition to the vessel wall[62,63]. This may reflect inappropriate patient selection, with the deployment of endoluminal devices in less than ideal aneurysm morphology, or malpositioning of the device early in the learning curve of endoluminal operating experience[30]. In some instances component failure and subsequent graft migration may contribute[53]. Many of these endoleaks can be treated by additional endovascular procedures[19,64,65]. The long-term results of treating late endoleaks are not available.

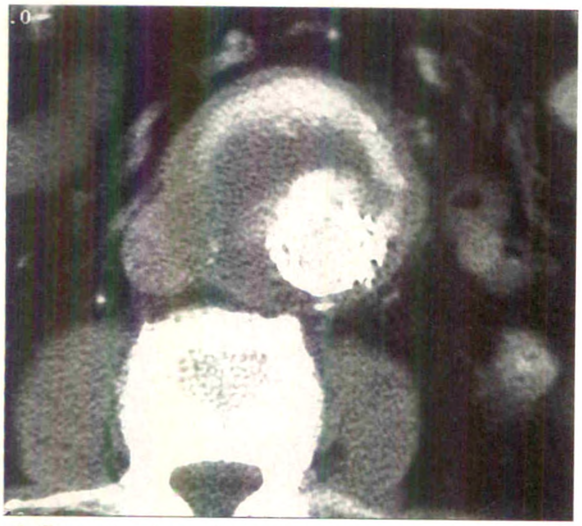

Fig. 2 Contrast-enhanced computed tomogram following endoluminal repair of abdominal aortic aneurysm. The presence of an endoleak is confirmed by the pool of white contrast agent within the excluded aneurysm sac

Effect of endoluminal grafting

In addition to a reduced postoperative hospital stay following endoluminal AAA repair, a number of authors have reported that successful AAA exclusion is accompanied by a reduction in the diameter of the aneurysm sac on follow-up CT[39,63,66,67]. This reduction in diameter is not seen in cases of endoleak or collateral perfusion[63,67] and may prove to be a useful indicator of these complications during routine follow-up. Paradoxically, it has also been noted that the reduced AAA diameter is accompanied by a dilatation of the proximal aortic neck at the site of proximal device fixation[62,66]. If this dilatation is progressive, it may result ultimately in device migration at the proximal neck, with subsequent endoleakage and failure to maintain aneurysm exclusion. Further long-term follow-up studies will clarify this issue.

The future

The encouraging results of the early studies should ensure the continued development and improvement of endoluminal devices. Endovascular AAA repair is unlikely to become exclusively percutaneous if it is to be applied to as broad a spectrum of aneurysm morphology as possible and if the risks of embolic complications are to be minimized. However, it is likely that improved device design will enable a significant number of procedures to be performed percutaneously.

The requirement for precise preoperative imaging in endoluminal AAA repair makes the technique of little value (with currently available devices) in the acute situation of rupture, where one might expect the benefits of the technique to be the greatest[20]. Nevertheless, it may be appropriate to treat a leaking aneurysm in the haemodynamically stable patient by endoluminal methods. The technique may also have a role in the treatment of thoracic aortic aneurysm[45], where the benefits of endoluminal surgery may be even more marked than in the abdominal setting. The success of endoluminal surgery depends on appropriate patient selection. Undertaking endoluminal surgery in patients with inappropriate aneurysm morphology will increase both the primary failure rate and the incidence of late endoleaks. It may

Table 5 Causes of late failure reported following endoluminal repair of abdominal aortic aneurysm

					Endoleak				
Reference	Year	Total no. of late failures	Graft thrombosis	Graft infection	Fixation site failure	Device migration	Fabric failure	Lumbar or mesenteric backbleed	Further endoluminal treatment successful
Blum *et al.*[39]	1997	9	0	0	0	0	6	3	7
Parodi *et al.*[42]	1997	16	0	0	16	0	0	0	2
Chuter *et al.*[30,52]	1997	14	5	1	2	4	0	2	2
Moore and Rutherford[53]	1996	7	0	0	5	0	0	2	0
Lawrence-Brown *et al.*[13]	1996	7	3	0	4	0	0	0	0
White *et al.*[45]	1997	6	0	0	6	0	0	0	2

Endoleak refers to clinical failure of endoluminal surgery because of leaks persisting or arising *de novo* more than 6 months after graft implantation[23] not prove possible to increase the proportion of patients suitable for endoluminal AAA repair above the 30–50 per cent currently quoted[33,38,39]. While this figure can be increased by treating smaller aneurysms whose morphology is more suited to successful endoluminal repair[42,68], there is no justification for this approach until the results of endoluminal surgery are improved significantly.

Data regarding the suitability of an AAA for endoluminal surgery are currently based on the experience of tertiary referral centres with considerable referral bias. Having demonstrated that endoluminal AAA repair is feasible in selected patients who would previously have undergone open repair, it is important to determine the percentage of aneurysms currently undergoing open surgical repair that would be suitable for endoluminal repair. This has not been done outwith the aforementioned highly selected patient populations, and a determination of how widely applicable this new technique will be, based on currently accepted indications for AAA repair, is required to allocate resources properly.

Considerable concern remains about the long-term outcome of endoluminal surgery. The durability of devices currently undergoing evaluation is unknown and component failure has already led to design revision[53]. Increased length of follow-up will probably reveal design weaknesses in other devices, and many revisions and modifications will be required before the ideal endoluminal device is developed.

Persisting or late-onset endoleak is associated with continued aneurysm expansion[60] and fatal rupture[30], and the outcome of treated and untreated endoleaks will be a major factor in determining the future of endoluminal repair. A recent comparison between endoluminal and open AAA repair in one centre has indicated that, although postoperative survival is similar between patient groups, survival with a successful outcome (continuing graft function without endoleak) is significantly higher following open AAA repair[69]. It therefore remains imperative that long-term follow-up data are available from a number of centres before undertaking randomized controlled trials of endoluminal AAA surgery *versus* conventional repair.

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Review

Lymphocyte function in wound healing and following injury

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Background Injury activates a cascade of local and systemic immune responses.

Methods A literature review was undertaken of lymphocyte function in wound healing and following injury.

Results Lymphocytes are not required for the initiation of wound healing, but an intact cellular immune response is essential for a normal outcome of tissue repair. Injury affects lymphocyte immune mechanisms leading to generalized immunosuppression which, in turn, increases host susceptibility to infection and sepsis. Although the exact origin of post-traumatic immunosuppression remains unknown, stress hormones and immunosuppressive factors, such as inflammatory cytokines, prostaglandin E_2 and nitric oxide, affect lymphocyte function adversely. Post-traumatic impairment of T lymphocyte immune function is reflected in decreased lymphocyte numbers, as well as altered T cell phenotype and activity. Antibody-producing B lymphocytes are variably affected by injury, probably secondary to alterations of T lymphocyte function, as a result of their close interaction with helper T cells. Therapeutic modulation of the host immune response may include non-specific and specific interventions to improve overall defence mechanisms.

Conclusion Early resuscitation to restore lymphocyte function after injury is important for tissue repair and the prevention of immunosuppression.

Injury elicits local repair mechanisms and a systemic defence response in which cytokines and other metabolic products of activated lymphocytes can act either beneficially to provide enhanced host resistance or deleteriously to depress the function of remote organs and cause systemic inflammation. After minor injury the systemic host response may be negligible; severe trauma, however, is associated with altered metabolism characterized by catabolism and wasting of lean body mass, and a compromised immune system. Delayed death after trauma, occurring days to weeks after injury, is attributed to abnormalities of the immune system, leading to infection.

Non-specific host defence mechanisms include polymorphonuclear and mononuclear phagocytes, natural killer (NK) cells and products of complement activation. Specific defence mechanisms include antibody formation by B lymphocytes, direct microbial killing by T lymphocytes and T lymphocyte activation of mononuclear phagocytes. Changes in leucocyte numbers and function may reflect both the cause and the effect of infection, sepsis and injury. What follows is a review of the immune response to injury in general, followed by a discussion of lymphocyte function in wound healing and after injury.

Non-specific defence

Immune response following injury affects innate and adaptive immunity. The innate or non-specific antigenic features include intact physical barriers of skin and mucous membranes, the alternate pathway of complement activation which is spontaneously active in plasma and can opsonize or destroy bacteria while sparing host cells, and immune-competent cells and their soluble mediators. Cellular elements include macrophages, neutrophils, NK cells and endothelial cells. Antigenic products from pathogenic organisms or arising from tissue destruction activate defence mechanisms. Activated cells of the innate immune system in turn synthesize potentially toxic mediators, including cytokines, such as tumour necrosis factor (TNF) α, interleukin (IL) 1 and IL-6, as well as kinins, platelet activation factor, eicosanoids and radicals (e.g. hydrogen peroxide and nitric oxide). Normal cellular and humoral immune function is necessary to restore host integrity; overwhelming inflammatory response, however, leads to immune dysfunction and increases susceptibility to infection and sepsis.

Complement activation

The initiating factors are many but the subsequent inflammatory responses are qualitatively similar. Damaged tissue, foreign material or bacterial lipopolysaccharide can activate the alternate complement pathway. Complement activation results in assembly of C5b–9 (membrane attack complex) on the surface of Gram-negative bacteria with lysis of the bacteria after successful attachment. Products of the activated complement system, such as C3a and C5a, increase capillary permeability and play an important role in the initiation of the chemotaxis process[1,2]. Following burn injury, altered concentrations of complement components and altered leucocyte function have been reported[3,4]. Clinically, increased levels of C3a and membrane attack complex have been found to be associated with the development of multiple organ dysfunction following trauma[5].

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Phagocytic cells

Fixed phagocytic cells, such as dendritic cells and macrophages, are the first line of cellular defence. Phagocytosis and intracellular killing are the hallmark of the non-specific immune response. To facilitate antigen engulfment, opsonization of foreign protein must occur, a process in which foreign particles are coated with plasma cell-derived immunoglobulin and/or activated components of the complement system. The coated antigen is then bound to the Fc or complement receptors on the phagocytic cell, facilitating uptake. In addition to Fc and complement receptors, macrophages have on their surface receptors that recognize various microbial constituents, including the macrophage mannose receptor, CD14, a molecule that binds bacterial lipopolysaccharide, and the leucocyte integrin CD11b–CD18, also known as Mac-1[6,7]. The second important effect of the interaction of macrophages with pathogens is the secretion of cytokines; this is induced by bacteria binding to macrophage receptors. Important macrophage-derived cytokines (monokines) which occur in response to bacterial products include IL-1, IL-6, IL-8, IL-12 and TNF-α. The combined local effect of these mediators contributes to the local reaction to injury in the form of an inflammatory response. Systemically, these inflammatory monokines initiate an acute phase response, leading to the release of acute phase proteins from the liver, neutrophil mobilization from the bone marrow, protein mobilization from muscle and other effects.

Impaired function of the phagocytic cell system after injury was demonstrated more than 20 years ago[8,9]. Altered monocyte function is reflected in the altered release of soluble mediators[10]. Also, with respect to adaptive immunity, macrophages are antigen-presenting cells that are crucial for the activation of antigen-specific T cells. Macrophages efficiently ingest pathogens and are induced by infectious agents to express major histocompatibility complex (MHC) class II molecules and costimulatory activity. Following both experimental and clinical injury, antigen presentation and MHC class II molecule expression have been shown to be depressed, leading to impaired immune response[11].

Polymorphonuclear leucocytes

Circulating polymorphonuclear leucocytes are recruited at the site of inflammation by soluble mediators, causing cell adherence, transcapillary migration and chemotaxis. CD11b–CD18 is the ligand for the endothelial cell-expressed intercellular adhesion molecule 1, and this interaction causes the tight adhesion that is necessary for transmigration of neutrophils into the surrounding tissue[12,13]. Clinically, increased neutrophil CD11b expression has been demonstrated after major trauma and in patients with sepsis[14,15]. In severe illness endothelial cell activation is not confined to the original site of injury. In patients with peritonitis and multiple organ dysfunction syndrome (MODS), extensive expression of endothelial leucocyte adhesion molecule 1 occurs in endothelium remote from the abdomen and in the absence of bacteria in the areas examined[16]. Sequestration of neutrophils and leucostasis have been demonstrated both during hypovolaemic shock and after reperfusion[17,18]. Activated neutrophils release inflammatory mediators, such as oxygen radicals and proteases, leading to endothelial cell swelling and organ damage. After severe injury neutrophil function may be compromised, contributing to postinjury immunosuppression[19–21].

Natural killer cells

NK cells, non-T, non-B lymphoid cells bearing no known antigen-specific receptors, play an important part in innate immunity. The exact mechanism by which these cells distinguish between infected and uninfected host cells is not completely clear. It appears, however, that cytokine-activated NK cells selectively kill target cells bearing low levels of MHC class I molecules[22]. Also, infected cells bound by antibodies may be destroyed by NK cells, a phenomenon known as antibody-dependent cell-mediated cytotoxicity (ADCC). ADCC seems to be mediated by the FcγRII receptor (CD16) on NK cells[23]. Suppressed NK cell activity has been reported following both experimental and clinical injury[24–26], suggesting that impaired NK cell function may contribute to increased susceptibility to post-traumatic infection. Non-adaptive immune mechanisms play an important role both on their own, in controlling infection in its early phase while the adaptive lymphocyte-mediated immune response is being developed, and also through their impact on the adaptive immune response.

Role of lymphocytes in wound healing

Tissue injury initiates a cycle of inflammation, cellular migration and replication, and connective tissue deposition and remodelling, to restore tissue integrity. It is clear that T cells play a modulatory role in wound healing, although the full range of their effects is incompletely understood. There is no evidence that B lymphocytes play a significant role in wound healing[27]. Histologically, significant numbers of T lymphocytes appear in rat wounds around the fifth day after wounding, peaking around day 7[28,29].

T cell function in wound healing

Direct evidence for lymphocyte involvement in the control of wound healing is provided by studies examining the effects of *in vivo* lymphocyte depletion. Global T cell depletion, using the 3OH12 monoclonal antibody against the Thy 1.2 antigen, causes a marked reduction in mechanical strength and collagen content of a wound[30]. Anti-Lyt2 antibody-induced depletion of the CD8$^+$ subset causes marked enhancement of wound healing[31]. These findings suggest a possible role for CD8$^+$ cells in the overall downregulation of wound healing activity. It might be expected that CD4$^+$ T helper cells would promote such activity. Depletion of this subset by an anti-L3T4 antibody, however, has no effect on either mechanical strength or collagen formation[31]. Therefore, an incompletely characterized lymphocyte population bearing the all-T cell antigenic marker Thy 1.2, but not the mentioned determinant for CD4 or CD8, seems to be responsible for the promotion of wound healing, as its depletion impairs wound healing (*Fig. 1*).

Support for these findings is provided by experiments in congenitally athymic nude mice[32]. These animals have a profoundly impaired T cell-dependent system and display significantly enhanced wound breaking strength and collagen deposition in response to injury, compared with normal thymus-bearing animals. T cell reconstitution of

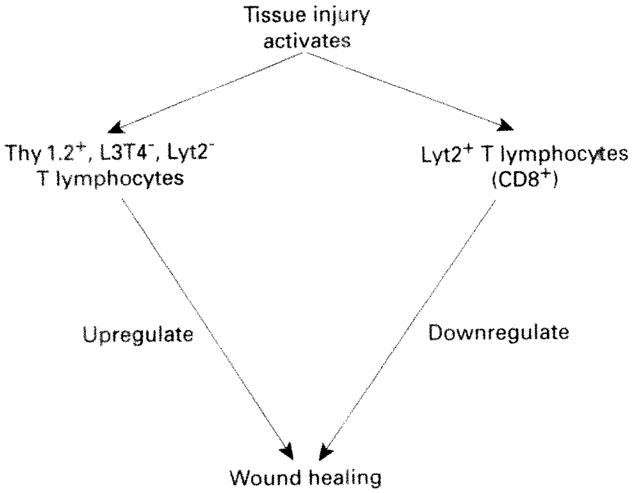

Fig. 1 Proposed role of T lymphocytes in wound healing. A T cell population (Thy 1.2$^+$, L3T4$^-$, Lyt2$^-$ seems to promote wound healing. Lyt2$^+$ T cells (CD8$^+$) appear to downregulate wound healing, as their depletion enhances wound mechanical strength and collagen formation

nude mice with syngenic splenic T lymphocytes results in a significant decrease in mechanical strength and collagen formation, to values similar to those observed in normal euthymic controls. This supports the hypothesis that a subset of T cells normally plays a downregulatory role in wound healing.

Some information regarding the role of T lymphocytes in wound repair has been obtained from *in vivo* studies which used lymphotrophic or lympholytic agents[33]. The parenteral or enteral administration of agents known to enhance thymic and T lymphocyte function, such as growth hormone[34], vitamin A[35] or arginine[36], leads to an increase in mechanical strength and collagen deposition. Agents that suppress T lymphocyte function, such as steroids and retinoic acid, markedly impair wound healing[35]. In addition, systemic treatment with cyclosporin and tacrolimus (FK506), both immunosuppressive drugs known to inhibit T cell proliferation and IL-2 synthesis by interfering with intracellular calcineurin, leads to impaired wound healing in rats[37,38]. Wound nitric oxide synthesis, which has been shown before to be critical for normal healing[39], is decreased by treatment with tacrolimus. Thus, impaired healing by tacrolimus may be a reflection of diminished wound nitric oxide synthesis.

Modification of T lymphocyte function by adult thymectomy, which prevents the induction of CD8$^+$ T cells, causes an increase in the mechanical strength of wounds[40]. This effect can be reversed by intraperitoneal placement of autologous thymic grafts in thymectomized rats. Conversely, administration of thymic hormones, such as thymulin or thymopentin, results in impaired wound healing as assessed by mechanical strength and collagen deposition[33]. These data suggest that the thymus has an inhibitory effect on healing.

Role of lymphokines in wound healing

The T cell contribution to the healing process is mediated, in part by the release of soluble factors (lymphokines) (*Table 1*). A variety of *in vitro* and *in vivo* studies has tried to elucidate the role of lymphokines in fibroblast regulation and in *in vivo* tissue repair.

In vitro *studies.* Many lymphokines are capable of modulating fibroblast replication, migration or collagen synthesis *in vitro*. Some, such as transforming growth factor (TGF) β or interferon (IFN) γ, are well characterized, whereas many other mediators that can modulate *in vitro* fibroblast activity remain incompletely characterized. Both inhibitory and stimulatory lymphokines for all aspects of fibroblast function have been described. While the *in vivo* regulation of wound healing probably consists of a complex multifactorial interaction between various cytokines and growth factors, including the T cell-derived lymphokines, it remains unclear how these factors act in temporal sequence and in concert.

In vitro, TGF-β is a potent fibroblast chemotactic molecule which stimulates collagen and fibronectin synthesis, and enhances collagen–matrix contraction by fibroblasts[41,42]. TGF-β, however, does not have a significant growth enhancing effect on fibroblasts. In doses greater than 100 ng/ml it appears to inhibit fibroblast growth[43]. This suggests that the major role of TGF-β is to halt proliferation and stimulate important effector functions of the fibroblast, such as collagen synthesis. TGF-β also induces monocyte chemotaxis and secretion of fibroblast growth factors, including IL-1.

Fibroblast activating factor (FAF), which stimulates fibroblast proliferation, has been described in humans and guinea-pigs, and is produced by activated lymphocytes[44]. IFN-γ, on the other hand, is a potent inhibitor of fibroblast proliferation and collagen synthesis[45]. TNF-α, released by macrophages and activated lymphocytes, induces the proliferation of growth-arrested fibroblasts in a dose-dependent manner (10–500 ng/ml)[43]. In doses greater than 500 ng/ml there is an apparent suppression of fibroblast growth by TNF-α as a result of cell death. In the presence of high concentrations of TNF-α and indomethacin, an inhibitor of prostaglandin (PG) E_2 synthesis, the cells remain viable but no longer proliferative. This suggests that in high doses TNF-α-induced fibroblast cytotoxicity is in some way prostanoid mediated. TNF-α has been shown to inhibit collagen and fibronectin synthesis by fibroblasts, and to diminish endothelial cell proliferation[46].

It is evident that lymphokines can exert both stimulatory and inhibitory signals on all aspects of fibroblast activity, and there seems to be a balance between these effects. While knowledge of how this balance is achieved is scant, it is clear that an imbalance may result in wound failure or, conversely, in excessive fibrosis. It has been demonstrated that the continued presence of antigenic stimulus at a healing site leads to excessive fibrosis, presumably due to continued activation of T lymphocytes with unchecked production of FAF[47].

In vivo *studies.* The presence of a number of lymphokines has been confirmed at the wound site *in vivo*. In a murine model, the presence of biologically active IL-1, TNF-α and IL-6 has been demonstrated, while IL-2, IL-3 and IL-4 could not be detected[48]. In addition, TGF-β occurs in significant quantities although biological activity is uncertain[49].

Another approach to the assessment of the role of lymphokines in wound healing is to administer recombinant factors *in vivo*, either locally or systemically, and to examine the response of wounds. Application of TGF-β to linear incisions in rats leads to increased mechanical strength and collagen deposition, with a concomitant rise in mononuclear cell and fibroblast infiltration[50,51]. It appears that the concentrations and ratios of the different TGF-β subtypes 1, 2 and 3, and their corresponding receptors at the wound site, seem greatly to influence the effect of this lymphokine on collagen quality and quantity. Interestingly, the exogenous addition of neutralizing antibody to TGF-$\beta_{1,2}$ reduces scar formation after cutaneous injury in rats[52]. Early application of this neutralizing antibody to an incisional wound reduces the degree of macrophage infiltration at the wound site, neovascularization, and the amount of fibronectin and collagen, without reducing the tensile strength of the wound. It also improves the architecture of the neodermis to resemble that of the normal dermis and thereby reduces scarring.

Systemic administration of human recombinant IL-2 to rats increases the mechanical strength of wounds with an associated rise in collagen deposition[53]. Wound fluid, on the other hand, contains an IL-2 inhibitory factor which has been postulated as playing a role in the down-regulation of the exuberant cell proliferation and activity that characterizes the early phases of wound healing[54].

The administration of IFN-γ via subcutaneously implanted osmotic pumps in mice results in a decrease in the thickness and collagen content of the capsule that forms around the pumps[55]. The *in vivo* abrogation of endogenous TNF-α by topical application of anti-TNF-α polyclonal antiserum results in a significant increase in collagen deposition[56]. Also, in a different study, when TNF-α was applied topically, decreased mechanical strength of incisional wounds in rats was noted[57]. Hypertrophic scars on the other hand have been demonstrated to contain fewer TNF-α-producing cells[58], suggesting that physiological TNF levels may play an important role in the downregulation of excessive collagen production in wounds.

Clinical trials investigating the effect of cytokines and growth factors on healing have focused mainly on chronic wounds. Since 1986, when it was first demonstrated that locally acting growth factors may promote healing of chronic cutaneous ulcers in patients[59], numerous clinical studies have been conducted using either autologous platelet-derived or recombinant growth factors. Improved healing has been reported by several authors[60–62], whereas others have found no beneficial effects from the topical treatment of chronic wounds with growth factors[63–65]. Several multicentre trials are now under way to confirm or refute these findings from small studies. Part of the

Table 1 Effects of lymphokines on immune and wound cells

Lymphokine	Abbreviation	Cellular effects
Interleukin 1	IL-1	Stimulates leucocyte chemotaxis, keratinocyte migration, fibroblast proliferation
Interleukin 2	IL-2	Stimulates T cell growth, promotes T helper cell activity, augments cytotoxicity, stimulates B cell differentiation
Interleukin 3	IL-3	Stimulates both T and B cell maturation and mast cell growth; multipotential haemopoietic cell growth factor
Interleukin 4	IL-4	Stimulates T and B cell and mast cell growth, B cell antibody production, inhibits macrophage activation
Interleukin 5	IL-5	Stimulates B cell growth and antibody production, enhances eosinophil differentiation
Interleukin 6	IL-6	Stimulates T and B cell activity, inhibits fibroblast proliferation
Interleukin 8	IL-8	Stimulates leucocyte chemotaxis and activity
Interleukin 10	IL-10	Inhibits cytokine release by type 1 T helper lymphocytes and macrophages
Interferon γ	IFN-γ	Stimulates macrophage activity and B cell differentiation, stimulates and inhibits fibroblast proliferation, inhibits collagen production and collagen cross-linking, inhibits endothelial cell proliferation, increases endothelial cell adhesivity for lymphocytes
Tumor necrosis factor α	TNF-α	Stimulates neutrophil and macrophage activity, inhibits collagen synthesis by fibroblasts, inhibits endothelial cell proliferation, stimulates fibroblast proliferation
Lymphotoxin (tumour necrosis factor β)	LT (TNF-β)	Inhibits B cell growth, stimulates fibroblast proliferation and collagen synthesis
Transforming growth factor β	TGF-β	Inhibits B cell growth, T cell and macrophage activation, activates neutrophils, stimulates fibroblast migration, stimulates and inhibits fibroblast proliferation, stimulates fibroblast collagen synthesis, inhibits endothelial cell proliferation
Granulocyte–macrophage colony-stimulating factor	GM-CSF	Stimulates B cell differentiation, inhibits T cell growth, stimulates growth of mixed colonies of granulocytes and macrophages from bone marrow progenitor cells
Fibroblast inhibition factor	FIF	Inhibits fibroblast migration
Fibroblast inhibitory factor	IF	Inhibits fibroblast proliferation
Fibroblast activating factor	FAF	Stimulates fibroblast proliferation and collagen synthesis
Macrophage chemotactic factor	MCF	Stimulates macrophage migration
Macrophage inhibitory factor	MIF	Inhibits macrophage activity
Macrophage activating factor	MAF	Stimulates macrophage activity

explanation for the conflicting results so far may be the lack of appreciation of the complex pathophysiology of non-healing wounds, the heterogeneous groups of patients used and pharmaceutical considerations[66].

Thus T lymphocytes and their soluble mediators have been demonstrated, both *in vitro* and *in vivo*, to possess the capacity to modify essential steps in the process of wound healing. Defined subsets of T cells express stimulatory or inhibitory effects on repair mechanisms and take part in a balanced system of wound cell regulation. An intact cellular immune response appears to be critical for the successful outcome of healing.

Immunosuppression after injury

The immune response after injury involves the release and interplay of numerous soluble mediators (*Fig. 2*), which may act in an endocrine, paracrine or autocrine fashion. Also, their cellular sources are diverse, including hormone glandular cells, immune-competent inflammatory cells and mesenchymal cells.

Stress hormones

Following injury several endogenous hormones are released into the systemic circulation, including catecholamines and glucocorticoids. This neuroendocrine response adversely affects both the humoral and cellular immune systems. Catecholamines impair T cell proliferation, IL-2 receptor expression and immunoglobulin production by B lymphocytes[67–69].

Glucocorticoids are known to impair the phagocytic activity of polymorphonuclear leucocytes[70], and to decrease T cell blastogenesis and IL-2 production, leading to impaired cellular immunity[71]. They also affect macrophage function, leading to decreased expression of the Ia antigen (murine MHC class II equivalent) and IL-1 synthesis[72]. Bilateral adrenalectomy abolishes the fall of both T and B lymphocyte numbers in the circulation after injury, indicating that stress hormones play a significant role in these changes[73].

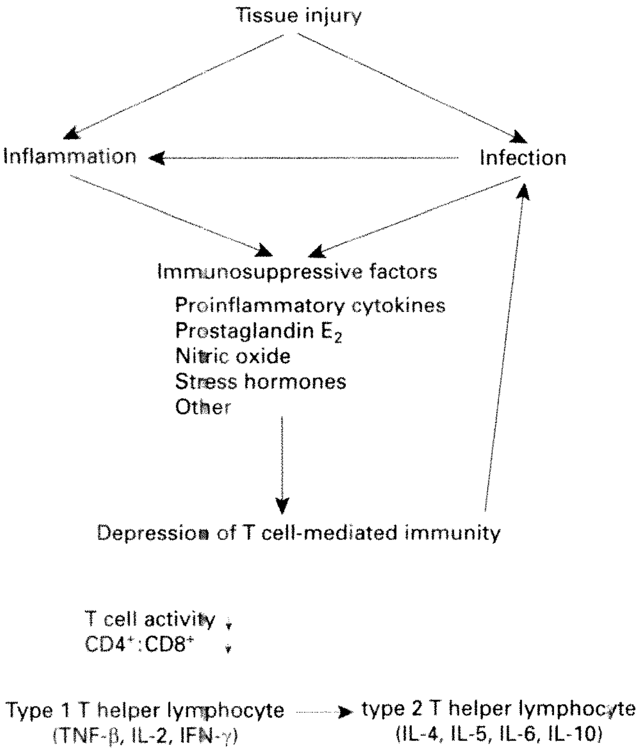
Tissue injury
Inflammation
Infection
Immunosuppressive factors
Proinflammatory cytokines
Prostaglandin E_2
Nitric oxide
Stress hormones
Other
Depression of T cell-mediated immunity
T cell activity ↓
$CD4^+:CD8^+$ ↓
Type 1 T helper lymphocyte (TNF-β, IL-2, IFN-γ)
type 2 T helper lymphocyte (IL-4, IL-5, IL-6, IL-10)

Fig. 2 Systemic effect of trauma on T cell-mediated immunity IL, interleukin; IFN, interferon; TNF, tumour necrosis factor

Immunosuppressive factors

Trauma is associated with impaired response to delayed-type hypersensitivity skin tests[74], decreased rate of allograft rejection[75] and enhanced tumour growth[76], all of which depend on intact T cell function. A feature common to all these injured states is the presence of wounded tissue. Not only is there evidence to suggest that the incidence of post-traumatic immunosuppression is related to the extent of the injury, but also that there is a direct relationship between the extent of injury and the incidence of post-traumatic septic complications and mortality[76–79]. Patients who became septic after burns all showed immunosuppressive serum preceding or coinciding with the septic episode[77]. A vicious circle may occur in which immunosuppressive factors initiate and propagate the systemic inflammatory response and host infection, leading to the production of new immunosuppressive factors.

If the wound is, indeed, a potential source of factors that contribute to alterations in immune function, it might be expected that the extracellular wound fluid that collects at the site of repair would be rich in such factors. Support for this hypothesis is provided by a number of *in vivo* studies examining the effect of parenterally administered extracellular wound fluid in normal animals. Intraperitoneal administration of wound fluid collected from 10-day-old wounds inhibits *in vivo* allogenic responses, as assessed by skin graft rejection, compared with autologous serum injection[80]. Also, *in vivo* administration of wound fluid impairs the immune responses to sepsis[81].

The wound factors responsible for these immunosuppressive effects have only been characterized incompletely. Prostaglandins and many of the cytokines produced by inflammatory cells have immunosuppressive qualities. PGE_2, a metabolite of the arachidonic metabolism, has an immunoinhibitory effect on cell-mediated immunity[82]. PGE_2 production by mononuclear cells occurs after burns and traumatic injury[83]. Increased production of PGE_2 adversely affects antigen presentation by macrophages via a depression of Ia antigen expression (murine MHC class II equivalent) in a dose-dependent manner. In addition, PGE_2 exerts a downregulatory effect on TNF-α and membrane IL-1 expression by macrophages[84], thereby interfering further with a membrane protein that is important for adequate antigen presentation. This is thought to be mediated through a PGE_2-induced increase in intracellular adenosine 3′, 5′-cyclic monophosphate (cAMP) levels. A similar mechanism may occur in the depression of IL-2 production by T lymphocytes[85]. In septic injury, decreased T lymphocyte proliferative activity is caused, at least in part, by impaired intracellular calcium ion^{+} mobilization. This may be a consequence of PGE_2 activation of the secondary messenger cAMP, which can antagonize calcium signalling in T cells[86,87]. In addition, it appears that PGE_2 is an important costimulator for the shift of type 1 towards type 2 T helper lymphocyte phenotype, leading to decreased IL-2 and IFN-γ activity[88].

The presence of other serum depressive factors known as 'suppressive active (glyco-)peptides' has been reported in the serum of patients with burns or other trauma. These peptides may suppress T and B cell proliferation and inhibit IL-2 production by concanavalin A-stimulated peripheral blood T lymphocytes. The molecular weight of these immunosuppressive substances ranges between 2000 and 600 000 Da, but the best described have a molecular weight of less than 20 000 Da[89].

Proinflammatory cytokines, such as IL-1, IL-6 and TNF-α, are derived mainly from activated macrophages and, when produced in excessive amounts, contribute to the immunosuppression observed following trauma[90,91]. Release of these endogenously derived proinflammatory mediators is currently thought to be responsible, at least in part, for the early activation of the acute phase response, and to play a central role in the beneficial and adverse sequelae of infection and injury[92].

Increased levels of TGF-β, known mainly as a growth factor involved in tissue repair mechanisms, are associated with impaired T cell function and immunosuppression during sepsis[93] and after injury[94]. Similarly, levels of IL-10, a cytokine shown to inhibit type 1 T helper cell and macrophage function, are raised in patients soon after surgery[95]. Some investigators, however, have demonstrated decreased IL-10 production by splenocytes isolated from septic and injured animals[96]. Neutralization of endogenous IL-10 increases TNF synthesis and mortality in animal models of endotoxaemia[97] and peritonitis[98], but increases survival in a model of pneumonia[99]. Recently, Hauser *et al.*[100] reported increased levels of IL-10, but not of IL-4 or TGF-β_1, in human soft tissue haematomas associated with fracture, providing further evidence that immune modulatory factors may collect at the site of injury[100]. The exact role of IL-10 in post-traumatic and septic immunosuppression, however, remains unclear. It should be emphasized that these cytokines may not only mediate deleterious effects on host integrity during the systemic inflammatory response but also represent important regulators of the normal immune response. Also, both experimentally and clinically, alterations in cytokine concentrations and activities often represent both the cause and effect of immunosuppression after injury, making the assessment of their role in the immune response difficult.

Soluble receptors to TNF-α and other proinflammatory cytokines have been isolated in the circulation of patients after trauma and are thought to represent a regulatory tool for the inhibition of the actions of these cytokines[101]. Soluble forms of cytokine receptors seem to be structurally identical to the extracellular portion of the cytokine-binding domains of these receptors[102,103]. This may be an example of autoregulation of the immune system. Whether the expression of these soluble receptors results in pathological immunosuppression or, more likely, improves post-traumatic immune defence by neutralizing excessive proinflammatory cytokines, remains unclear. It appears that soluble mediators of cellular interactions may exert beneficial or detrimental effects on host defence function, depending on their concentrations and their interplay within the cascade of cytokine reactions during the inflammatory response.

There is, therefore, strong support for the hypothesis that overspill of the wound environment into the general circulation has a role in the induction of post-traumatic immunosuppression. Not only is a number of potent immunosuppressive factors present in the wound, but there is evidence of alteration in immune activity at sites remote from the wound. Further support for this hypothesis is provided by the fact that the appearance and degree of post-traumatic immunosuppression correlates with the extent of the initial injury. In addition, it is well known that the early removal of damaged and/or infected tissue can prevent or diminish immunosuppression after injury[104]. It may well be that, in the presence of major tissue damage and the need for extensive wound repair, the processes that are normally limited to the site of healing spill into the general circulation and have multiple, possible undesirable, consequences on normal immune responsiveness.

Table 2 Lymphocyte dysfunction after injury

Impaired CD4^{+} T cell activity
Impaired CD8^{+} T cell activity
CD4^{+}:CD8^{+} ratio reduced
Appearance of immature T cells
T helper lymphocyte shift from type 1 (tumour necrosis factor β, IL-2, interferon γ) to type 2 (IL-4, IL-5, IL-6, IL-10)
Loss of recall antigen responses (anergy)
Impaired B cell function and immunoglobulin production
Decreased natural killer and lymphokine-activated killer cell activity

IL, interleukin

Lymphocyte function following systemic injury

Injury not confined to the initial site of insult affects the immune response via both cellular and humoral immunity (*Table 2*). This in turn may increase susceptibility to infection and death from sepsis[73,105].

T lymphocyte function following injury

The first evidence that the cell-mediated immune response was impaired in traumatized patients was published 50 years ago[106]. After injury, alterations of T lymphocyte immune function may be a result of lymphocyte subpopulation changes, as assessed by differential expression of surface markers, as well as a result of cell activity changes. Alteration of cell activity may be assessed by the response of lymphocytes to *in vitro* activation by mitogen, lymphokine synthesis, and expression of surface markers and receptors.

Decreased lymphocyte proliferation in response to mitogenic stimulation occurs after surgical procedures, accidental trauma, burns and haemorrhage[107–109]. This effect usually lasts for several days after injury, despite maximum resuscitation and normal recovery[110,111]. Both clinical and experimental studies have demonstrated that this impairment of T cell proliferative response is associated with an increased susceptibility to infection and death[105,111,112].

Lymphocyte subtypes. Lymphocyte function is determined in large part by the antigens displayed on the cell surface. These surface antigens control cellular interactions and regulate biochemical activities in the cytoplasm, thereby determining the cell's functional response. The specific nature of the T cell response appears to be controlled by the T cell receptor–CD3 complex. The coreceptor molecules CD4 and CD8 bind MHC class II and class I molecules respectively, and act synergistically with the T cell receptor in signalling, resulting in an increase in the sensitivity of T lymphocytes to antigen[113,114].

Following injury, alterations in lymphocyte numbers and subset proportions have been described in different lymphoid compartments. Lymphocytes from bone marrow, peripheral blood, spleen and thymus are decreased after thermal injury, but lymph nodes draining a wound contain a severalfold increase in their number of lymphocytes[15]. Immune alterations after thermal injury and decreased lymphocyte numbers in different organs after injury may be due, at least in part, to a redistribution of the lymphocyte pool. Following traumatic injury[79] and burns[116], the absolute number of lymphocytes decreases in the circulation, the decrease in the proportion of $CD4^+$ lymphocytes being greater than that of $CD8^+$ lymphocytes. Thus, there is a shift from the normal ratio of $CD4^+$ cells to $CD8^+$ cells (2:1 in human circulation), to a greater proportion of $CD8^+$ T cells. In rodents, the injection of $CD8^+$ T cells predisposes to increased mortality when the animals are subjected to septic insult[117]. The *in vivo* administration of a monoclonal antibody directed against such $CD8^+$ cells in burned animals improves survival following a bacterial challenge. This finding further substantiates the important role of $CD8^+$ T cells in burns. In contrast, others have found a relative decrease in the $CD4^+:CD8^+$ ratio only in animals with infection; this was not present in thermal injury without infection[118]. This is consistent with results in patients with trauma[119] and in haemorrhaged mice[20]; neither show changes in the numbers or proportions of $CD8^+$ or $CD4^+$ cells. At present it remains controversial whether injury is associated with altered $CD4^+:CD8^+$ ratios. There may be a difference between burned patients, and patients after non-thermal injury and haemorrhage. Also, it is not clear whether this alteration of $CD4^+:CD8^+$ ratio is cause or effect in the context of infection. Feeney *et al.*[121] reported decreased numbers of $CD4^+$ and $CD8^+$ cells in acutely ill patients admitted to the intensive care unit for medical or surgical reasons. However, depression of T cell numbers was unpredictable and did not correlate with severity of illness, predicted mortality rate or actual mortality rate.

As naive $CD4^+$ T lymphocytes differentiate, they become either type 1 or type 2 T cells, characterized by the pattern of lymphokines they secrete (*Fig. 3*). Type 1 helper cells transcribe and translate messenger RNA (mRNA) for TNF-β, IFN-γ and IL-2, and regulate T cell-mediated macrophage activation. The counterpart of type 1 subgroup is the type 2 subgroup. Through the elaboration of IL-4, IL-5, IL-6 and IL-10 (but not TNF-β, IFN-γ or IL-2), type 2 helper cells are involved in B cell differentiation and the humoral immune response.

Following injury, in addition to decreased numbers of T helper cells, there is a shift in the type 1:type 2 T helper cell balance towards a dominance of type 2, leading to downregulation of cell-mediated and, in some cases, upregulation of antibody-mediated immunity[122–124]. *In vivo* treatment with IL-12, a cytokine that induces a shift from the type 2 towards the type 1 T helper lymphocyte phenotype, increases survival after major trauma. This treatment with IL-12 is accompanied by increased IL-2 and IFN-γ and decreased IL-4 production by splenocytes[122,125].

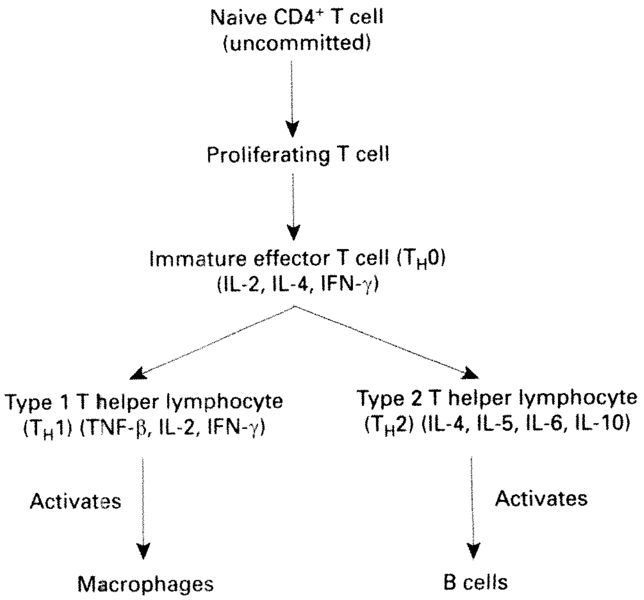
Naive CD4⁺ T cell
(uncommitted)
Proliferating T cell
Immature effector T cell (TH0)
(IL-2, IL-4, IFN-γ)
Type 1 T helper lymphocyte
(TH1) (TNF-β, IL-2, IFN-γ)
Type 2 T helper lymphocyte
(TH2) (IL-4, IL-5, IL-6, IL-10)
Activates
Activates
Macrophages
B cells

Fig. 3 Stages of activation of $CD4^+$ T lymphocytes. Naive $CD4^+$ cells are thought to pass through an intermediate stage, the immature effector T cell (T_H0). T_H0 cells express some effector functions of both type 1 and type 2 helper cells. The T_H0 cells then differentiate into type 1 or type 2 $CD4^+$ T cells, characterized by the pattern of lymphokines they secrete. Selective activation of type 1 cells leads to cell-mediated immunity, whereas selective formation of type 2 cells promotes humoral immunity. IL, interleukin; IFN, interferon; TNF, tumour necrosis factor

The response to traumatic and thermal injury in humans involves the appearance in the peripheral blood of immature T cells that may express T6, T9, T10 and Ia1 surface antigens. These cells may be present in quantities otherwise seen only in malignant disease[126]. During infection, lymphocytes harvested from burned animals demonstrate altered intracellular metabolism, including rate of glucose and amino acid utilization, and decreased levels of adenosine deaminase, an immunologically important enzyme for lymphocyte activity[127].

Lymphokines. Ex vivo, the T cell receptor complex may be stimulated by different mitogens such as phytohaemagglutinin or concanavalin A, leading to effector responses by all T cells bearing this T cell receptor complex[114]. Mitogen and/or antigen-activated T lymphocytes produce IL-2. T cell activation, on the other hand, requires synthesis of regulatory cytokines, mainly IL-2, and expression of the corresponding cytokine receptor[128]. Experimentally, exogenous IL-2 improves cell-mediated immune response against infection[129]. Following injury, both human and animal studies have shown decreased IL-2 synthesis and IL-2 mRNA expression by T cells[107–109]. This diminished T cell ability to excrete IL-2 may be noted as long as 60 days after injury[130]. In burned mice the principal cellular abnormalities that result in altered T cell activation and IL-2 production lie downstream of the initiating signal transduction events and before IL-2 gene transcription[109,110]. A defect that involves the membrane receptors as well as the cytoplasmic cascade may explain why decreased IL-2 secretion can be only partially reversed by direct stimulation of the cytoplasmic components[131]. It has been suggested that the defect of the intracellular signal transduction pathway occurs at the calcium ion signal step and/or in the upstream signalling component effecting protein tyrosine phosphorylation[132].

For normal T cell function, IL-2 receptor expression and the cytoplasmic cascade following receptor activation appear to be as critical as the expression, synthesis and excretion of IL-2 itself[128]. However, results from studies investigating the effect of injury on IL-2 receptor expression are conflicting. Following injury, expression of the IL-2 receptor is reported to be decreased[83,131], increased[133] or unchanged[110,134].

After haemorrhage the production of other lymphokines, including IL-3, IL-5 and IL-6, is depressed[108,120]. IL-3 supports the survival, growth and differentiation of multipotential stem cells, and of erythroid and myeloid progenitor cells. Thus, the depression of IL-3 may have a direct effect on a variety of different cellular components involved in cell-mediated immunity, including the recruitment and maturation of monocytes and lymphocytes. IL-5 depression, similarly, may have a direct immunosuppressive effect on lymphocyte response to injury, as IL-5 stimulates B lymphocyte growth and antibody production, and enhances eosinophil differentiation. The proinflammatory cytokine IL-6 is produced early in the response to injury[90]. As IL-6 plays an important role in B cell activation, depression of this lymphokine may have important implications for the development of a competent humoral response. This is in keeping with depressed B cell responsiveness after injury[135].

IFN-γ activity is reported to increase or decrease after haemorrhage and to decrease after accidental injury[108,120]. IFN-γ is recognized as an important upregulator of macrophage function and, depending on the condition, may either stimulate or suppress B cell proliferation and differentiation. The marked decline in the capacity of T cells to produce IFN-γ after injury would be expected to lead to the impairment of macrophage activation as well as activation of cytotoxic T cells. There is evidence that the expression of human leucocyte antigen (HLA)-DR receptors on monocytes, which is coded by the MHC class II and needed for antigen presentation to T cells, decreases after trauma[136]. In addition, depressed levels of IFN-γ result in impaired T cell response to antigen and diminished monocyte antigen presentation[10].

Lymphocytes and nitric oxide. The activation of cytokine-inducible nitric oxide synthase (iNOS) during septic injury leads to the production of large quantities of nitric oxide, a recently discovered radical and biological mediator which can be toxic. Lymphocyte proliferative activity is impaired by macrophage-derived nitric oxide[137]. After burn injury, suppressed lymphocyte proliferation improves after *in vitro* addition of *N*-monomethyl-L-arginine (L-NMMA), a competitive inhibitor of NOS. This indicates a possible lymphocyte immunosuppressive role for nitric oxide in major injury[138]. When a panel of cloned T cells was examined, it appeared that type 1 T helper cells could be induced to produce nitric oxide, whereas type 2 T helper cells could not[139]. Secretion of IL-2 and IFN-γ by the cloned type 1 T helper cells was enhanced in the presence of L-NMMA, but was significantly inhibited by the addition of the nitric oxide donor, S-nitrosyl penicillamine, suggesting that nitric oxide may exert a self-regulatory effect on type 1 T helper cells. Other authors have proposed that nitric oxide may support a type 2 lymphocyte immune response. Mutant mice, lacking in iNOS, develop a significantly stronger T helper 1 type immune response, show reduced non-specific inflammatory response to carrageenin and are resistant to lipopolysaccharide-induced death[140].

In an animal study investigating the role of nitric oxide in the local inflammatory response, treatment with L-NMMA caused a significant reduction in T cell activity, measured by the production of IL-2 and IFN-γ, and T cell proliferation[141]. This suggests that nitric oxide may promote T cell activity in this model. It has also been demonstrated that nitric oxide is produced by mitogen-stimulated human peripheral blood mononuclear cells and that its production is essential for optimal proliferation[142]. The apparent contradiction in the effect of nitric oxide on T cell activity may be well due to the dual effect of nitric oxide on T cell proliferation. Low nitric oxide concentrations may be required for a normal T cell response, whereas high concentrations may inhibit cellular proliferation. A similar dual role for nitric oxide in the regulation of cell activity has been reported in studies investigating the effect of nitric oxide on protein synthesis by mesenchymal cells. Low nitric oxide concentrations appear to promote collagen synthesis, whereas higher levels inhibit protein and collagen production[143,144].

B lymphocyte function following injury

B lymphocyte-derived immunoglobulins mediate the humoral component of the specific immune response. The proportion of B cells that actively produce immunoglobulins is small, usually less than 1 per cent of the total number of plasma cells. After systemic infection there is amplification of this proportion, with the percentage of the total plasma cell repertoire specifically directed in this manner being as high as 10 per cent. Antibodies protect the host from infection by pathogen neutralization, opsonization or complement activation. Antibody response to antigens, however, requires T cell help[145]. B cells are recognized by T helper cells when antigen bound by surface immunoglobulins is internalized and returned to the cell surface as peptide bound to MHC class II molecules. The interaction of an antigen binding B cell with an armed T cell leads to the expression of the B cell stimulatory CD40 ligand on the helper T cell surface and to the secretion of stimulatory cytokines[146]. B cell differentiation is regulated mainly by the type 2 T helper lymphocyte phenotype, characterized by the expression of IL-4, IL-5 and IL-6[147]. Although armed T helper cells are required for B cell responses to protein antigens, certain bacterial products, such as lipopolysaccharide, can induce B cell proliferation and differentiation in the absence of T cells[148].

The plasma cell antibody response may be affected at many steps in the B cell activation process. Alterations in B cell antigen presentation may result in decreased T cell help via the MHC class II antigen and impaired release of T cell-derived lymphokines. Decreased numbers of B cells capable of developing into immunoglobulin-synthesizing plasma cells will result in impaired antibody response. Like the overall host defence, B cell maturation and B cell response to infection have been shown to be affected by injury.

B cell differentiation may be assessed by examining the spontaneous and cytokine- or mitogen-induced immunoglobulin production by B cells *in vitro*. Spontaneous production of immunoglobulin (Ig) G in culture by B lymphocytes isolated from the peripheral blood of patients after trauma is increased[149] or unchanged[150], while spontaneous production of IgM is decreased[150] or unchanged[149]. Pokeweed mitogen (PWM) or *Staphylococcus aureus* Cowan I antigen-induced secretion of IgG and IgM has also been variously reported as enhanced or reduced. *In vitro* addition of indomethacin has no effect on decreased PWM-induced IgM and IgG secretion, suggesting that the suppressive effect is not PGE_2 mediated[150]. However, the addition of normal T lymphocytes or supernatants from antigen-stimulated T cells to B cells enhances the antibody response to PWM, suggesting that the impaired B cell response after trauma may be due to failure of T cell help[150].

The spontaneous expression of CD23, a B lymphocyte activation antigen, is reduced on B cells from burned patients[133]. Also, decreased antibody response to viral immunizations occurs in children with blunt trauma[151]. DNA synthesis in B lymphocyte mitogen-stimulated cultures, however, is increased in burned patients, but decreased in those with trauma[150].

Major trauma and minor injury or stress in mice results in a gradual fall in the level of B lymphocytes, with the maximal drop 2 h after the operation or handling procedure. Numbers return to normal within 24 h of both minor and major trauma[73]. In healthy adult patients undergoing nephrectomy as transplant donors, no changes in immunoglobulins are found, but total B cell numbers fall[152]. Haemorrhage causes a decrease in serum immunoglobulin levels, as well as decreased numbers of B cells secreting antibody[135]. There may be a change in B cell repertoires after haemorrhage, so that in the week after haemorrhage there are fewer pre-B cells present potentially to become plasma cells producing antibody against bacterial antigens. Thermal injury is associated with decreased serum IgG levels[153]. IgA and IgM levels are not affected except when burn eschar is infected with fungus, when IgM levels rise.

It appears that the function of antibody-producing B lymphocytes is variably affected by traumatic injury. Many reported effects may not be discussed in isolation, without examining changes in T lymphocyte function. Because B cell function is directly affected by cytokine production by macrophages and T lymphocytes, as well as by interactions with antigen-specific helper T cells, abnormalities in any of the steps in the B cell activation cascade may result in a diminished B cell response. In this way impaired B lymphocyte function will be secondary to alterations of T lymphocyte and macrophage function following trauma.

Therapeutic immunomodulation

Therapeutic modulation of the immune system following injury ranges from basic interventions designed to restore homoeostasis with aggressive resuscitation and nutritional support to the latest state-of-the-art manipulations of immune cell activity and its products. The following focuses on some approaches that may currently be undertaken to alter host immune function in the clinical setting.

Nutrition

The relationship between nutrition and immunity has been investigated extensively in the past. Acute protein calorie malnutrition is known to depress cell-mediated immune response[154]. Nutritional repletion can restore some of the abnormalities, as assessed by total lymphocyte count, mitogen responsiveness and skin-test reactivity. The hypermetabolic state associated with acute injury imposes a significant strain on the patient's nutritional reserves, with a substantial effect on the immune system. Immediate nutritional support after trauma reduces the incidence of septic complications and mortality[155]. The route of administration and composition of nutritional formulas seem to be important, with enteral feeding apparently superior to parenteral nutritional support, leading to improved cell-mediated immune function, reduced septic complications and shorter hospital stay[156,157]. In addition, early rather than delayed, and supplemented rather than standard, diets are associated with better outcome[158–161]. There is evidence that supplemented enteral nutrition commenced before operation has some benefits over solely postoperative feeding[162].

Several specific supplemental nutrients have been identified recently as offering specific immunomodulatory properties. Often these nutrients are used in amounts well in excess of normal nutritional requirements and so they are said to possess a 'pharmacological' effect, in order to differentiate the situation from standard nutritional use. Such nutrients include arginine, glutamine, ω-3 polyunsaturated fatty acids and nucleotides.

In animal studies, arginine supplementation improves survival after burns and intra-abdominal sepsis[163,164]. In addition, exogenous arginine improves the healing of skin wounds in both rodents and humans[165,166]. Lymphocyte blastogenesis and T helper cell numbers are increased in patients after surgery who receive arginine supplementation[167].

Glutamine is the most abundant amino acid in the body, accounting for approximately 20 per cent of the total circulating free amino acid pool and for more than 60 per cent of the free intracellular amino acid pool. It is an important vehicle for nitrogen transfer between tissues. Glutamine is also a regulator of protein synthesis and an essential precursor for nucleotide biosynthesis in all cells. It serves as an energy fuel for the gut mucosa and other rapidly dividing cells, such as fibroblasts, lymphocytes and epithelial cells[168]. Trauma, severe illness and sepsis are followed by a rapid fall of muscle and plasma glutamine levels[169,170]. For this reason the clinical application of glutamine has been pursued and some efficacy has been shown in clinical outcome, including improved postoperative nitrogen balance[171]. In patients after bone marrow transplantation, a reduced incidence of infection and a shortened hospital stay are associated with glutamine supplementation[172].

The amount and type of dietary lipids can profoundly influence immune response and resistance to infection. Lipids become incorporated into phospholipids of cell membranes and other components within cells, thereby influencing structural integrity, transport systems, membrane fluidity, receptor expression and cell–cell interactions. Diets high in ω-3 polyunsaturated fatty acids (found in fish oils) appear to have some beneficial effects on immunosuppression following injury, and have been reported to be superior to conventional diets containing mainly ω-6 polyunsaturated fatty acids (found in vegetable oils)[173]. Although there is controversy concerning the immunomodulatory mechanisms of such diets, a reduction in immunosuppressive eicosanoid release (e.g. PGE_2) and an altered profile of inflammatory cytokines (e.g. TNF-α, IL-1, IL-6) seem be responsible for the observed phenomena.

Ribonucleic acids are essential for cellular turnover and protein synthesis. In conditions of severe stress, dietary supplementation with nucleotides appears to reverse some aspects of immunosuppression[174,175].

Several of these immunostimulatory dietary components have been combined to evaluate their total immunological and metabolic effects in the clinical setting. In the treatment of severely burned patients a low-fat enteral diet supplemented with 0·4 per cent arginine, 0·25 per cent cysteine and 0·5 per cent ω-3 fatty acids reduces wound infection and length of stay, compared with other standard enteral formulations[176,177]. In another prospective trial, surgical patients undergoing operation for upper gastrointestinal malignancy were randomized to receive either a supplemented (arginine 12·5 g/l, RNA 1·25 g/l and ω-3 fatty acids 1·7 g/l) diet or a standard enteral diet after surgery[161]. Septic complications and length of hospital stay were reduced in the supplemented group. Similar results, including increased numbers of lymphocytes, decreased infection rates and length of stay, have been documented by others[158,178].

Cytokine modulation

Immune dysfunction in states of profound stress is characterized by impaired balance of immunosuppressive and counter-regulatory influences. Much effort has been expended in interfering with early inflammatory events thought to set the stage for the subsequent generalized inflammatory response. Immunomodulatory therapy has focused on strategies designed to inhibit TNF, IL-1 and IL-6, using cytokine antibodies, receptor antagonists or soluble receptors. Anticytokine therapy has been successful in animal models. In clinical studies, however, results are less convincing[179,180]. No improvement in survival has been noted; indeed an increased mortality rate was reported in patients receiving high doses of recombinant human TNF receptor[181]. Use of an IL-1 receptor antagonist, however, has yielded some promising early results in humans[182]. In a randomized human phase III study increased survival has been documented, but only in a retrospectively defined subset of high-risk patients[183]. Distinct survival advantages have yet to be demonstrated by randomized prospective trials using anticytokine therapy in the clinical setting.

Granulocyte colony-stimulating factor (G-CSF) for sepsis prophylaxis in neutropenic patients (e.g. patients receiving chemotherapy for cancer) is well established. However, the use of G-CSF following injury is experimental. In patients with burns, leucocyte function improves and white blood cell count is increased after G-CSF treatment[184]. Lipopolysaccharide-induced release of proinflammatory cytokines (TNF-α, IL-1β) from blood cells was attenuated in volunteers pretreated with G-CSF[185], suggesting that there may also be some prophylactic properties of G-CSF against sepsis in non-neutropenic patients.

Immune suppression following injury is reflected in polarization of the helper T cell activity with a shift in the type 2 T helper cell direction[122,124]. Impaired type 1 T helper cell activity is reflected in decreased synthesis of IL-2 and IFN-γ. The inability to produce adequate amounts of IL-2 results in an incomplete proliferative T cell response to antigenic stimuli, whereas the lack of IFN-γ results in inefficient macrophage antigen presentation[10]. Attempts have therefore been made to modulate the cell-mediated immune response by administration of these lymphokines to animals and humans. The administration of IL-2 appears to enhance survival in animals with intra-abdominal sepsis. It is most effective when given at the site of infection and probably acts by stimulating local host defences[186]. There are as yet no reliable data from human studies using IL-2 as an exogenous immunostimulatory agent after injury.

Exogenous IFN-γ increases resistance to intra-abdominal sepsis, and improves survival after trauma and haemorrhagic shock[187]. In humans, IFN-γ reverses the trauma-induced suppression of MHC class II HLA-DR antigens on macrophages[188]. However, no clear benefit in sepsis-related morbidity or mortality has been demonstrated in patients given IFN-γ[189]. Recently, treatment with IL-12, a cytokine that induces a shift from the type 2 towards the type 1 T helper lymphocyte phenotype, has been reported to increase survival after major trauma in animals[125]. IL-12 treatment resulted in increased IL-2 and IFN-γ production by splenocytes.

Non-steroidal anti-inflammatory drugs

PGE_2 production from arachidonic acid by activated monocytes–macrophages is proposed as one of the most critical immunosuppressive pathways after injury[188], affecting both humoral and cellular immune function. After severe trauma, upregulated PGE_2 synthesis lasts for as long as 21 days[83]. Cyclo-oxygenase-inhibiting non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or indomethacin, restore some of the immunosuppressive effects following trauma. In animals, ibuprofen and indomethacin are effective in reducing PGE_2, preventing depressed T cell proliferation[86], improving antigen presentation by macrophages and synthesis of IL-1 and TNF, and maintaining lymphocyte IL-2 and IFN-γ production[190,191]. Their use is associated with improved organ function and survival following septic shock[192,193]. In septic burned rats, however, ibuprofen decreases the survival rate[194]. In patients with major trauma or following operation, indomethacin seems to improve the cellular immune response, including increased IL-2, IL-1 and TNF-α release[195,196]. A significant increase in the CD4:CD8 ratio was shown by Gogos *et al.*[197]. Improvement of haemodynamic and pulmonary function in septic patients by ibuprofen treatment has been reported by others[198]. Deterioration of renal function, found in some animal studies, and integrity of the gastric mucosa are concerns when NSAIDs are used routinely in the compromised patient. Adequate fluid resuscitation and cytoprotective agents may ameliorate certain of these effects, but the use of NSAIDs cannot be endorsed unequivocally. Further studies are required.

Thymomimetic agents

Thymic hormones promote the cytokine-mediated regulation of T cell development in precursor cells and also the proliferative response of mature T cells in the periphery[199]. Different compounds, including the synthetic thymomimetic purines, such as isoprinosine and methylinosine monophosphate (methyl-IMP), and the pentapeptide TP-5, have been used in the past to modulate cellular immune function[200,201]. Further insight into the effect of thymic hormones on immune function and tissue repair mechanisms was obtained from studies using congenitally athymic mice, thymectomized adult animals and animals treated with thymic hormones[32,33,40]. Thymic hormones and CD8$^+$ T cells that are generated in the thymus downregulate the early cellular events of wound repair, leading to decreased collagen deposition and reduced wound mechanical strength. Methyl-IMP augments lymphocyte responses to T lymphocyte mitogens in rodents and humans. Also, delayed-type hypersensitivity is increased after methyl-IMP administration. Isoprinosine reverses *in vitro* immunosuppressive effects following trauma and burns[199].

TP-5 restores the *in vitro* lymphocyte proliferative response as well as the delayed-type hypersensitivity response after major surgery[202]. However, T cell receptor protection (CD3 and CD4) and restoration of IL-2 synthesis are not achieved with TP-5 alone. When TP-5 is combined with indomethacin, *in vitro* testing of lymphocyte function shows improved T cell reactivity compared with TP-5 alone[203]. These results indicate that simultaneous cyclo-oxygenase inhibition and T cell activation can enhance cell-mediated immune mechanisms following surgical trauma. TP-5 decreases mortality in burned[204] and septic[205] animals. In critically burned patients, however, a randomized trial failed to demonstrate improved mortality or rate of septic complications[206]. Overall, the clinical relevance of these observations remains doubtful, as data demonstrating improved morbidity and mortality in humans are lacking.

Immunoglobulins

The demonstration of impaired humoral immunity in sepsis and following major injury gave rise to numerous studies using immunoglobulins in an attempt to provide the patient with higher titres of antibodies against bacterial endotoxins and exotoxins, with or without increased opsonic activity. In addition, immunoglobulins may synergize with β-lactam antibiotics due to their content of antilactamase antibodies[207]. Both experimental and clinical trials suggest a protective effect of intravenous immunoglobulin preparations against various infections, using 5S and 7S immunoglobulin, IgG, IgM, IgG with IgM and IgA, and *Pseudomonas* immunoglobulin[208–215].

The beneficial effects of immunoglobulin treatment may be seen first through a reduction in the number of infectious and septic complications in surgical and polytraumatized patients and, second, through a reduction in the duration of mechanical ventilation and of treatment in the intensive care unit in patients with infectious complications after surgery. However, with regard to the ultimate endpoint of all sepsis and trauma trials – reduction in MODS and mortality – the results of most controlled clinical trials have been disappointing. In patients with severe postoperative sepsis, however, Dominioni *et al.*[209] have reported a reduction in the mortality rate from 67 to 38 per cent with IgG therapy. In a different study, in which E5, a murine immunoglobulin (IgM) antilipid A monoclonal antibody, or placebo was given to patients with suspected Gram-negative sepsis, the overall mortality rate was comparable between the two groups. In the subsets of patients with confirmed Gram-negative septic shock, mortality was slightly higher in the treated than in the placebo group, but significantly lower in treated patients with sepsis but no shock[211]. On the other hand, when HA-1A, a predominantly human IgM antiendotoxin monoclonal antibody, was used, the subgroup with Gram-negative bacteraemia, both with and without shock, had a lower mortality rate[215]. However, a subsequent multicentre trial with HA-1A was suspended when an interim analysis of data revealed a slight but not significant increase in mortality in non-bacteraemic patients[214]. A truly beneficial effect of immunoglobulin treatment in trauma and sepsis still remains to be proven.

Other therapeutic approaches and conclusion

A great variety of agents is being evaluated in experimental animals. Some, such as glucan (a potent macrophage stimulant)[216], ketoconazole (a thromboxane synthase inhibitor)[217] and antithrombin III[218], have shown promising results in clinical trials. More recently, nitric oxide, thought to play an important role in the septic state, has been studied extensively in animals and humans. Inhibitors of NOS have been used to reverse the haemodynamic changes caused by sepsis, but results are conflicting[219,220]. Nitric oxide inhibition causes an increase in mean arterial blood pressure and systemic vascular resistance, as well as a decrease in cardiac output and heart rate in patients with sepsis[221]. However, organ perfusion may be decreased by nitric oxide inhibition, leading to organ damage and increased mortality[222,223]. Although increased nitric oxide synthesis may cause hypotension in septic shock, nitric oxide also modulates the immune response, inhibits platelet and granulocyte adhesion, and seems to be an important mediator in the nervous system. So depending on dose and location, nitric oxide may exert both beneficial and detrimental effects on host integrity[224,225]. Also, because pure selective inhibitors of the different NOS isoforms (iNOS, neuronal constitutive NOS, endothelial constitutive NOS) are not available, further work needs to focus on the development of selective inhibitors which, when given at the right time and dose, may have beneficial effects on the outcome of septic states. In contrast to increased levels of nitric oxide in sepsis, nitric oxide production after trauma is decreased, which may contribute to increased susceptibility to infection[226]. Clearly, interventions affecting nitric oxide physiology must carefully take into account the differential role that nitric oxide may play in the immune response.

Of the different approaches currently being undertaken to modulate immune function following injury, only some can be recommended unequivocally: (1) early and complete resuscitation with restoration of organ perfusion; (2) aggressive wound debridement, particularly of burn wounds; (3) drainage of any septic focus and use of appropriate antibiotics; and (4) early enteral nutrition with consideration of specific nutritional supplements, such as arginine, glutamine, ribonucleic acids and ω-3 polyunsaturated fatty acids.

Early host support to modulate immune function after injury seems to be critical for the outcome after severe trauma. The basic scientific fields of cellular and molecular biology, immunology and medical genetics are increasing the understanding of immune dysfunction after injury and during sepsis, and are providing clinicians with new therapeutic tools. To date, however, most clinical trials of novel agents to treat sepsis and injury-related immunosuppression have failed to show clinical efficacy. This has occurred despite considerable animal data suggesting a positive therapeutic benefit.

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Review

Non-operative management of blunt hepatic trauma

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Background Non-operative management is currently considered the treatment of choice in over 50 per cent of adult patients with blunt liver injury. This report reviews the criteria for non-operative management and its potential downside.

Methods English language publications were reviewed.

Results Most reports from major trauma centres in the USA support the non-operative treatment of patients with blunt liver injury if well established criteria are met. Using such criteria, non-operative treatment is successful in 50–80 per cent of cases. Adjunctive radiological techniques may be helpful in managing some complications of non-operative treatment.

Conclusion Non-operative management is safe in haemodynamically stable patients with blunt liver injury. Computed tomography (CT) of the abdomen is extremely useful to document the extent of the damage and the presence of associated injuries, but it is not possible, based on CT alone, to predict failure; careful physiological monitoring in selected patients is indicated to avoid catastrophic complications.

The liver is the most commonly injured abdominal organ after penetrating and blunt trauma[1,2]. The widely variable nature of the injury contributes to the extensive literature on this subject and it is the main reason for the number of operative alternatives[3]. Over the past 10 years, there has been a dramatic change in the management of hepatic injury, specifically its non-operative management. Even though non-operative treatment has become the standard of care in children, its use in the adult population is surrounded by controversy. However, this approach, initially met with scepticism, is becoming the standard method of care in major trauma centres in the USA[1,4–7]. The main reasons behind the success of this approach include: (1) better imaging techniques, (2) clinical experience from abbreviated laparotomy and planned reoperation ('damage control')[8–10], and (3) a better understanding of the natural history of liver injury (i.e. bleeding, healing and complications).

At the University of Louisville there has historically been a great deal of interest in the management of hepatic injury[3,9–18] and, using that experience as well as an analysis of the current literature, the authors will: (1) review the surgical anatomy of the liver and its implications for the diagnosis and non-operative treatment of injury, (2) describe the current classification of liver injury based on organ injury scaling, (3) analyse the complications of non-operative management and their relationship to morbidity and death, and (4) describe the current criteria used in this non-operative treatment. Penetrating injury and surgical management of specific hepatic injuries are not discussed because such management has been more consistent over time.

Surgical anatomy

For the trauma surgeon, knowledge of the vascular supply of the liver and its relationship to the different segments and lobes is crucial in determining the best surgical alternatives at operation. After birth the umbilical vein obliterates, leaving the liver with two nutrient sources of blood, the splanchnic circulation through the portal vein and the hepatic artery. The dual blood supply merges in the hepatic sinusoids and is collected from this site into the hepatic veins that join the inferior vena cava (IVC) behind the liver. The blood supply divides the liver into right and left lobes, which cleave in a plane that passes from the bed of the gallbladder to the IVC. In the presence of active haemorrhage, surgical exposure of the hepatic veins is extremely difficult, but has become more feasible as a result of techniques developed in liver transplantation. The segmental distribution of the blood supply further divides the right lobe into anterior and posterior segments, and the left lobe into medial and lateral segments, along with the quadrate lobe anterior to the porta hepatis and the caudate lobe posterior to the portal vein[19]. The liver is surrounded and secured by numerous ligamentous structures, including the right coronary ligament, the right triangular ligament, the left coronary ligament, the left triangular ligament (which fuses as a single structure at the tip of the lateral segment of the left lobe to form the appendix fibrosa hepatis), and the falciform ligament (which contains the obliterated umbilical vessels in the ligamentum teres hepatis[20]). Treatment of hepatic haemorrhage often requires mobilization and elevation of the liver by ligamentous division.

Physiology

The main function of the liver is filtration, regulation of metabolic substrates, specific protein synthesis for

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coagulation, carrier protein synthesis and lipid metabolism. The liver also plays a significant role in glucogenolysis and gluconeogenesis, synthesis in the hepatocytes of very low density lipoproteins, and degradation of ammonia and its conversion to urea[19].

The hepatocyte phenotypically expresses more of the human genome than any other cell of the body by using virtually every enzyme, receptor and transport mechanism in the genetic code. The liver to date cannot be replaced by mechanical, physical or biochemical support that does not use viable hepatocytes. The anhepatic state is not compatible with life for extended periods; liver 'failure' and liver 'shock' are relative but overused terms describing compromise of any liver function. If the liver truly fails, death follows rapidly. However, the organ has the capability of regeneration, even after massive hepatic resection or after extensive injury[21].

Incidence, aetiology and associated injuries in liver trauma

Size and location make injury to the liver common: it occurs in 20, 30 and 40 per cent of patients operated on for blunt, gunshot and stab wounds respectively[20]. Overall, blunt injury, usually secondary to motor vehicle accidents, is the commonest cause. In a series of 136 patients reported by Croce *et al.*[5] in Memphis, Tennessee, 95 per cent of injuries were secondary to vehicle accidents, compared with 72 per cent of 404 patients in a multicentre review reported by Pachter and colleagues at New York University[22]. However, in another series of 1000 patients from Houston, Texas, Feliciano *et al.*[23] reported an incidence of 86 per cent of penetrating injuries, with only 14 per cent due to blunt trauma. A previous report from the same institution in 1976[24] described an incidence of 54, 31 and 15 per cent for gunshot wounds, stab wounds and blunt injuries respectively. In most parts of the USA and in Europe, however, such high numbers of penetrating injuries do not occur.

Injuries at other sites which are associated with penetrating trauma to the liver are common, occurring in up to 63 per cent of patients and mostly in the gastrointestinal tract[23]. After blunt hepatic injury, associated injuries are noted in 4–15 per cent of patients[25,26]. The association of diaphragmatic rupture with blunt hepatic injury has also been described, with an incidence of 3–9 per cent[25-28].

Current classification (Liver Organ Injury Scale)

Currently, hepatic injury is best described using the classification of the Organ Injury Scaling Committee of the American Association for the Surgery of Trauma (AAST). This was first outlined in 1989[29] and revised in 1994[30]. The advantage of this classification is the incorporation of both preoperative computed tomography (CT) and intraoperative assessment of extent of injury, including segmental anatomy (*Table 1*).

Diagnosis of liver injury

Peritoneal lavage

For the past quarter of a century, diagnostic peritoneal lavage has been used as the standard technique of choice for the diagnosis of acute intra-abdominal haemorrhage after blunt abdominal trauma[31,32]. It is fast, sensitive, accurate and relatively simple to perform. On the other hand, it is invasive, cannot diagnose retroperitoneal injury and is not a good predictor of therapeutic laparotomy. Non-selective exploratory laparotomy, performed on the basis of a positive lavage, results in a 3–25 per cent rate of non-therapeutic intervention[33], and some series have reported that half or more of hepatic injuries are not actively bleeding at the time of laparotomy[5,6,33].

Abdominal ultrasonography

Abdominal ultrasonography is accurate and useful in the evaluation of blunt abdominal trauma[34]. Most major trauma centres in the USA are moving towards the use of abdominal ultrasonography and CT as either an adjunct to or a replacement for lavage. In Europe and Japan, diagnostic abdominal ultrasonography has already replaced lavage as the diagnostic tool of choice[35,36].

Abdominal ultrasonography combines the advantages of lavage (fast and accurate) with those of CT (non-invasive and accurate). In a report by McKenney and associates[37] from the University of Miami, ultrasonography yielded a sensitivity of 88 per cent, a specificity of 99 per cent and an accuracy of 97 per cent in detecting intra-abdominal

Table 1 American Association for the Surgery of Trauma Organ Injury Scale: liver

Grade*		Description of injury†
I	Haematoma	Subcapsular, non-expanding, less than 10 per cent of surface area
	Laceration	Capsular tear, non-bleeding, less than 1 cm parenchymal depth
II	Haematoma	Subcapsular, non-expanding, 10–50 per cent of surface; or intraparenchymal, non-expanding, less than 2 cm in diameter
	Laceration	Capsular tear, active bleeding, 1–3 cm parenchymal depth, less than 10 cm in length
III	Haematoma	Subcapsular, greater than 50 per cent surface area or expanding; ruptured subcapsular haematoma with active bleeding; intraparenchymal haematoma greater than 2 cm or expanding
	Laceration	Greater than 3 cm parenchymal depth
IV	Haematoma	Ruptured intraparenchymal haematoma with active bleeding
	Laceration	Parenchymal disruption involving 25–50 per cent of hepatic lobe
V	Laceration	Parenchymal disruption involving more than 50 per cent of hepatic lobe
	Vascular	Juxtahepatic venous injuries (i.e. retrohepatic vena cava/major hepatic veins)
VI	Vascular	Hepatic avulsion

Reproduced from Moore *et al.*[30] with permission. *Advance one grade for multiple injuries to the same organ. †Based on most accurate assessment at autopsy, laparotomy or radiological study injury in 1000 patients. Despite its advantages, ultrasonography lacks organ specificity and it is operator dependent. At present, the authors believe that for haemodynamically unstable patients, ultrasonography is a good initial screening test after blunt abdominal trauma to document whether or not there is a large haemoperitoneum present.

Abdominal computed tomography

The single greatest factor permitting safe non-operative management of hepatic injury after blunt trauma is CT. However, it is haemodynamic stability and not the appearance of the liver on CT scans that determines which patients should be considered for observation alone. Many of the initial fears about non-operative treatment of stable patients have been alleviated by the recognition that CT can accurately delineate the anatomy of the injury, while providing crucial information about the amount of haemoperitoneum and the presence of associated intra-abdominal injuries. In this institution, after initial resuscitation, patients are given 25 ml MD-Gastroview (ditrizoate meglumine; Mallinckrodt Medical, St Louis, Missouri, USA) in 725 ml water by mouth or nasogastric tube. In addition, all patients receive 2 ml/kg ioversol (Optiray; Mallinckrodt Medical) intravenously. Rapid axial scans are performed on a GE HiSpeed Advantage Helical Scanner (General Electric, Milwaukee, Wisconsin, USA). Without optimal imaging by CT, safe non-operative management of blunt hepatic injury would not be possible. The role of CT continues to expand as technology advances and some reports have documented its potential role in penetrating injury of the right thoracoabdominal region in haemodynamically stable patients[38,39].

Laparoscopy

Diagnostic laparoscopy has been used successfully in penetrating trauma[40], but its place in blunt abdominal trauma is not well defined. It currently plays no significant role in the staging of blunt liver injury, although in therapeutic mode it can be useful for draining a retained haemoperitoneum or perihepatic collections after the non-operative treatment of severe liver injury.

Non-operative management of liver injury

Historically, operation has been the generally accepted method of treating blunt hepatic injury. At the time of surgical exploration, however, the injury is frequently found to be minor. No evidence of active haemorrhage is found in 50–80 per cent of patients[5,6,33] and the rate of non-therapeutic laparotomy in this group of patients may be as high as 67 per cent[6]. These two findings set the stage for an overall reassessment of the management of blunt hepatic trauma. Non-operative management has been the standard method of care of paediatric patients for the past 20 years, with a success rate of around 90 per cent[41–43]. Currently, in the adult population, non-operative management of blunt hepatic injury ranges from 50 to 82 per cent of all such injuries reported[6]. In a multicentre report of 404 patients, the incidence of non-operative treatment varied from a low of 20 per cent to a high of 70 per cent, with a mean of 47 per cent[22].

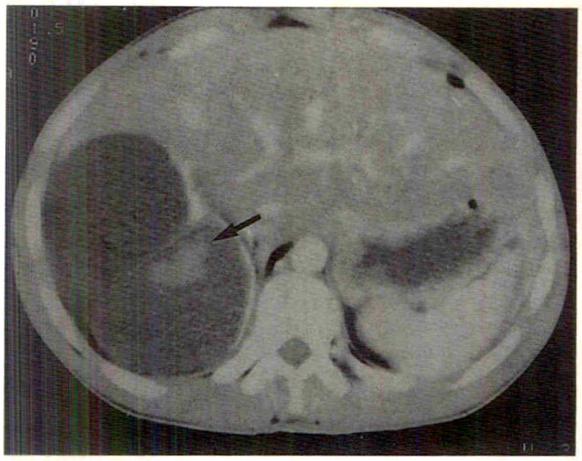

Fig. 1 Abdominal computed tomography demonstrating a large subcapsular haematoma and pooling of contrast agent (arrow), an indication of active intrahepatic haemorrhage

Criteria for non-operative management

Patients who are haemodynamically stable and who have no indications for laparotomy are ideal candidates for evaluation by emergency abdominal CT. In this select group, criteria for non-operative management include: (1) simple hepatic parenchymal laceration of intrahepatic haematoma, (2) absence of active haemorrhage (*Fig. 1*), (3) haemoperitoneum of less than 500 ml, (4) limited need for liver-related blood transfusions, (5) absence of diffuse peritoneal signs in patients not neurologically impaired, and (6) absence of other peritoneal injuries that would otherwise require an operation[21,44]. As previously noted, the results of conservative management of patients who meet these criteria have been excellent. As confidence has been gained with this management, the authors (and others) have expanded the acceptable volume of haemoperitoneum to 500 ml in haemodynamically stable patients[45]. More recently, Feliciano[46] has proposed non-operative management for any hepatic injury, regardless of its magnitude, if the patient is haemodynamically stable. This policy has been followed in a few strictly selected patients (*Fig. 2a*).

Failure of conservative treatment leads to surgery. An operation is required in patients who continue to need blood transfusion or whose vital signs deteriorate. Infection within the liver injury may also need a surgical solution. While increasing peritoneal signs and tenderness may be misleading, persistent or increasing abdominal pain should be treated with great caution.

Abdominal computed tomography follow-up

In complex hepatic injury, further evaluation with abdominal CT may by useful to document continuing haemorrhage which may cause otherwise unexplained blood losses, to document healing in extensive injury (*Fig. 2b*), and to evaluate the presence of intrahepatic or perihepatic fluid collections that may required percutaneous or laparoscopic drainage. Abdominal CT for documentation of liver wound healing before discharge from hospital, although desirable, is used inconsistently. In the multicentre review of 404 patients by Pachter *et al.*[22], 198 (49 per cent) underwent follow-up CT after the initial study; the timing of the repeat scan varied from 1 to 238 days. Of these 198 patients, 52 (26 per cent) underwent repeat scanning from 1 to 6 days after injury. Of these 52, only five showed any degree of resolution of the injury. Eighty-nine patients (45 per cent) underwent subsequent scanning from day 7 to day 10. Of these 89 patients, 69 (78 per cent) were noted to have had improvement of the original injury. Some of the authors of this multicentre review considered that, when injuries are not extensive (grades I–III), follow-up CT studies are superfluous. In another retrospective review of patients managed without operation, no statistically significant difference in outcome was found in patients with grade III or lower hepatic injury between one scan and more than one scan[47]. In this institution at present routine CT follow-up is individualized and not obtained routinely.

Relationship of computed tomography scan, organ injury and non-operative management

Conservative management of liver injury was described initially for grades I–III[22]. Currently, clinical experience shows that some haemodynamically stable patients with complex hepatic injuries (grades IV and V) may be safely managed without operation (*Fig. 2a*)[1,5,22,46,48]. However, in the multicentre review of 404 patients[22], 67 per cent who required an operation after failure of non-operative management were patients with grade IV or grade V injury. These are the patients who benefit from being closely observed in an intensive care environment. It is both the authors' experience and current clinical consensus that it is haemodynamic stability, rather than the extent of liver injury, that should determine whether or not a patient is managed without operation.

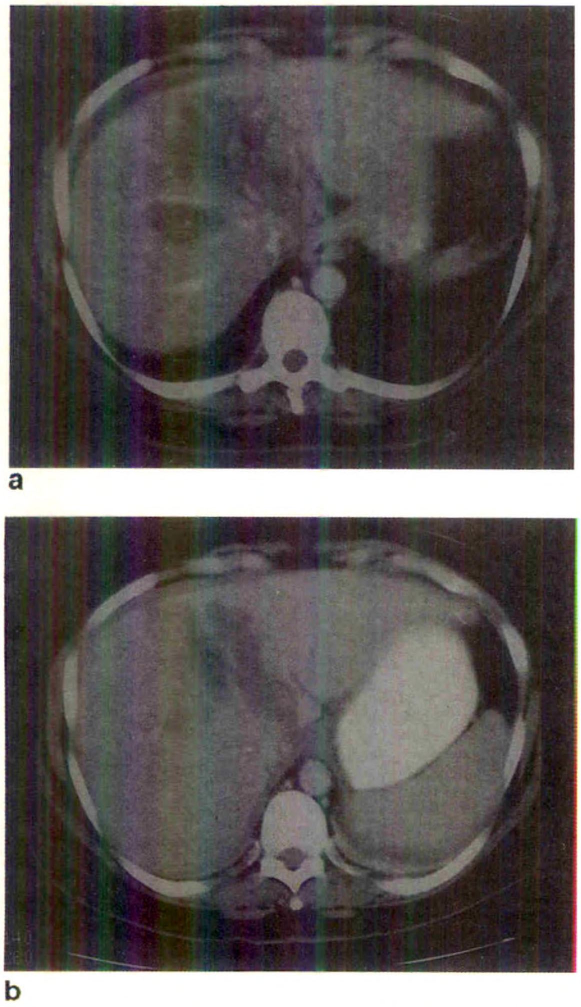

Fig. 2 a Extensive liver laceration (grade V) with no significant haemoperitoneum managed conservatively with no complications. b Follow-up computed tomography shows partial resolution of the haematoma and hepatic healing 7 days after the original injury

Resumption of normal activities

One of the most controversial issues regarding the non-operative management of hepatic injury is what constitutes an appropriate interval of time between the injury and resumption of normal activities, to avoid delayed haemorrhage. From a speculative standpoint, most clinicians have suggested that physical activities be limited and contact sports avoided for 3–6 months.

Two reports have indicated, however, that this time is probably too long. Karp *et al.*[41] documented almost complete liver restoration after 3–4 months. More recently, Dulchavsky *et al.*[49] demonstrated in an experimental model that, after 3–6 weeks, the wound-breaking strength of a hepatic injury equals that of uninjured liver. Their recommendation was that 'fear of reinjuring the liver injury allowed to heal by secondary intent should not limit the return of post-discharge activity beyond the normal restrictions recommended after any laparotomy'. It is known that a hepatic injury followed by serial CT shows healing by 3–4 months[45,50]. This may greatly underestimate wound-breaking strength and delaying return to full activity beyond this time seems unwarranted[1,22]. Currently, the authors advise patients to avoid contact sports or heavy physical activity for only 8 weeks after liver injury of grades III–VI.

Role of interventional radiology in blunt liver injury

Interventional radiology can be extremely useful: (1) to document active haemorrhage in subcapsular haematomas, (2) as a salvage alternative to surgery in the face of continuous haemorrhage in patients who remain haemodynamically stable, (3) in the diagnosis and treatment of haemobilia (*Fig. 3*), and (4) in the treatment of retained collections or perihepatic sepsis (using percutaneous techniques). Arteriography is useful in selected patients after operative perihepatic packing who have postoperative evidence of ongoing haemorrhage. Biliary endoscopy may be helpful in the diagnosis and treatment of complications secondary to complex liver injury[16,18].

Morbidity and death

Missed injuries

A major concern when treating hepatic trauma without operation is that of missing an injury. Some controversy originates from confusion between associated injury and a truly missed injury. The incidence of associated abdominal injury after blunt hepatic trauma in patients managed without operation ranges from 13 per cent[50] to 35 per cent[45]. However, the incidence of truly missed intra-abdominal injury ranges from 0·5 per cent[22] to 12 per cent[45] when abdominal CT is used, and from 5 to 15 per cent when CT is not performed[25,26]. In a review of 899

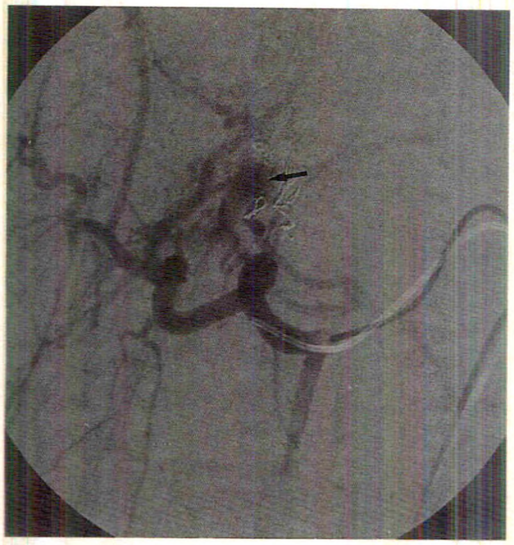

Fig. 3 Patient with haemobilia from a traumatic liver lesion (arrow) treated with embolization

patients, when strict guidelines for conservative management were followed and CT was used routinely, the incidence of missed injury was 0·2 per cent (two enteric injuries)[6]. It has also been reported that the most common cause of missed injury is wrong interpretation and poor quality of the initial scan. In their review of complex hepatic injuries, Pachter and Feliciano[6] emphasize that 'despite an accuracy rate of 97 to 99 per cent in detecting associated intraabdominal injuries, the CT scan is not infallible. Also it does not serve as a substitute for constant re-examination, preferably by the same set of examiners, of the patient whose abdominal examination remains equivocal in spite of a CT scan'. In patients for whom non-operative treatment of hepatic injury is chosen, the authors' current policy is to have a radiologist and the attending trauma surgeon read the initial CT scan, which must be of excellent quality, and all patients are admitted for observation under the care of the trauma service.

Delayed haemorrhage

Delayed hemorrhage is the most common complication of the non-operative management of hepatic injury and it is the usual indication for a delayed operation. In selected series, where strict guidelines for non-operative management were followed, the incidence of delayed haemorrhage ranged from 0 per cent[45,51,52] to less than 3·5 per cent[22,50], and blood transfusions were required in fewer than 20 per cent of those patients, with most requiring less than 4 units of blood[22,45,50–52].

Common treatment errors in patients with delayed haemorrhage are: (1) assuming that the haemorrhage is not related to the liver, (2) treating ongoing liver haemorrhage with multiple (more than four) blood transfusions in the hope that it will stop, (3) misreading the abdominal CT scan and underestimating the amount of haemoperitoneum or active hepatic haemorrhage (contrast 'pooling'), and (4) overestimating the amount of blood loss from associated injuries. The protocol in this trauma service for suspected haemorrhage in patients managed without operation indicates an immediate laparotomy or abdominal CT, depending on the haemodynamic stability of the patient (*Fig. 4*).

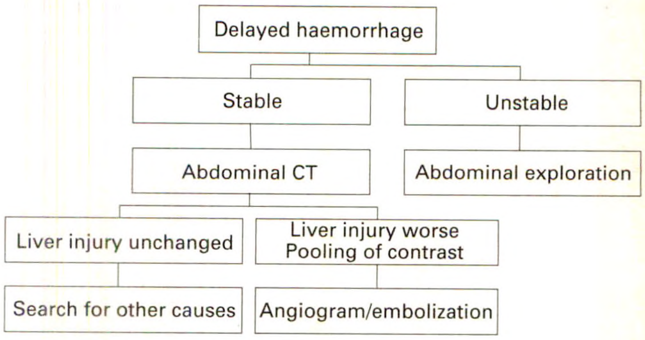

Fig. 4 Algorithm for management of delayed haemorrhage following blunt liver injury. CT, computed tomography

Biliary fistula and liver abscess

The incidence of biliary fistula in patients treated without operation after blunt hepatic injury ranges from 0·5 per cent[25,45] to 20 per cent[12]. This range is more a reflection of the methods used for diagnosis than of the true incidence. Available information indicates that most of these perihepatic collections are currently managed expectantly or by interventional radiologists using percutaneous techniques, with a success rate close to 70 per cent[22,45]. Patients with a well organized intrahepatic abscess may undergo a trial of medical treatment, with attempted percutaneous drainage. If there are no signs of improvement, or if fungi are isolated from the blood or the abscess site, more aggressive surgical treatment should be considered.

Haemobilia and bilhaemia

Intrahepatic artery pseudoaneurysm formation with haemobilia, classically described by Sandblom[53] as 'haemorrhage into the biliary tract', occurs when an injury or disease causes communication between the biliary tract and blood vessels. A history of abdominal trauma, jaundice, right upper quadrant colicky pain and blood in either vomitus or stool should point to this diagnosis. Iatrogenic causes are now most commonly encountered, as a result of percutaneous diagnostic and therapeutic procedures performed in the hepatobiliary system[54,55]. The management of haemobilia has evolved with the capabilities of interventional radiology. Once a pure surgical condition (including selective hepatic artery ligation and/or hepatectomy), haemobilia is now more often managed by percutaneous selective hepatic artery embolization (*Fig. 3*), with surgery reserved only for patients in whom such treatment fails[54,55], or for those with large intrahepatic cavities and/or sepsis[55,56]. When a surgical option is considered, vascular control should be obtained either by preoperative embolization or during surgery to avoid catastrophic haemorrhage. The incidence of haemobilia after conservative management of blunt hepatic injury is about 1 per cent[55] with most cases being secondary to blunt liver trauma[54,55].

Bilhaemia is an extremely rare complication of severe deceleration injury to the liver, in which the hepatic venules and the intrahepatic bile ducts rupture. This is followed by the formation of an extensive liver haematoma within necrotic tissue, leading to excessive serum bilirubin levels with only moderately raised levels of liver enzymes secondary to a traumatic intrahepatic biliovenous fistula. Progressive reabsorption of the cavity occurs in the ensuing days, with passage of bile from the disrupted bile ducts to the intrahepatic veins by a difference in gradient pressure of 15–20 cmH$_2$0 between the two systems (*Fig. 5a*). The ideal treatment of post-traumatic bilhaemia is by endoscopic sphincterotomy and biliary endostenting (*Fig. 5b*)[18]. Most current experience comes from Europe[57–59].

Extrahepatic bile duct stricture

Since more patients with complex hepatic injuries are being successfully treated conservatively and surviving[22], an increase in the number and complexity of complications secondary to non-operative management is likely. Recent reports[16,60–62] suggest that the incidence of biliary ductal disruption or intrahepatic ductal stenosis secondary to spontaneous healing of a severe liver injury is probably higher than has been appreciated previously. It is suspected that the risks of intrahepatic bile duct stenosis are even higher after extensive liver embolization to control haemorrhage in complex injuries. Because of the lack of experience with this uncommon condition, there is no uniformity of treatment criteria. Based on a limited experience with this rather uncommon complication[16], the authors believe that a conservative approach is warranted initially, leaving any surgical option as a late alternative.

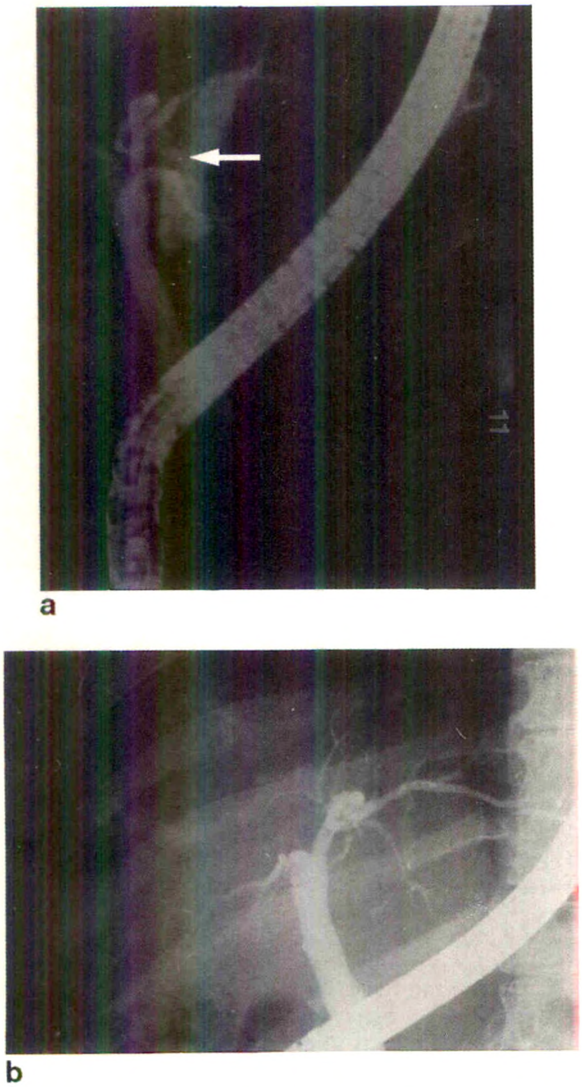

Fig. 5 Post-traumatic bilhaemia. **a** There is communication between the bile ducts and the hepatic veins (arrow). **b** Successful treatment with endoscopic biliary endostenting and sphincterotomy

Mortality rate

The overall mortality rate after blunt injury to the liver remains at 7–13 per cent, with most deaths resulting from associated injuries. The mortality rate arising from the liver injury itself is from 0 to 0·4 per cent in recent reports[5,22,45,63].

Future of non-operative treatment of liver injury

In 1908 Pringle[64] made the following observations: (1) bleeding from a significant liver laceration would not stop, (2) the liver would not heal, and (3) surgical intervention would be the only way to treat any liver injury. Based on these premises, hepatic injury has been managed surgically for the past eight decades. In the early 1970s, Richie and Fonkalsrud[65] and Popovsky and associates[66] reported the first successful non-operative treatment of liver injury. However, major changes in the conservative approach to hepatic injury started only in the early 1980s, with the report by Karp and associates[41] of non-operative management of hepatic injuries in 17 children. They hypothesized that liver repair proceeds in four stages: (1) resorption of blood, (2) coalescence of the laceration, (3) decrease in the size of the defect, and (4) restoration of liver homogeneity after 3–4 months. In the light of such observations and encouraging reports from many major trauma centres in the USA[5,22,44–46] and Europe[48,67,68], non-operative management of blunt hepatic injury in adults has increased dramatically in the past 10 years (*Table 2*). It is not now uncommon to read reports describing successful conservative management of blunt hepatic trauma in over 85 per cent of cases, and this is expected to be consistently over 90 per cent in the near future[4,22]. Nine of the authors' most recent ten patients with severe liver injury (grades IV and V) were successfully treated

Table 2 Evolution of non-operative management of adult hepatic trauma

Year	No. of patients	Hospital stay (days)	Transfusion (units)*	Success rate (%)
1988	20	13·3	4·0	90
1989	31	16·6	4·0	100
1990	84	11·5	2·0	95
1991	55	13·0	1·0	96
1992	93	13·9	1·3	95
1993	64	n.a.	n.a.	84
1994	148	16·2	1·6	95
1997	14	n.a.	n.a.	86

Data compiled from Pachter and Hofstetter[4], Farnell *et al.*[69], Mirvis *et al.*[33], Hiatt *et al.*[70], Frederico *et al.*[52], Knudson *et al.*[71], Pachter *et al.*[7], Durham *et al.*[45], Bynoe *et al.*[72], Hollands and Little[73], Hammond *et al.*[51], Sugimoto *et al.*[60], Boone *et al.*[74], Sherman *et al.*[50], Meredith *et al.*[1], Allins *et al.*[75]. n.a., Data not available. *A unit of transfusion is approximately 250 ml of blood without operation, with most patients requiring less than 500 ml of blood and staying in hospital for fewer than 10 days. On the other hand, it is important to emphasize that these results cannot be obtained unless the following criteria are met: (1) haemodynamic stability, (2) absence of peritoneal signs or localized only in the right upper quadrant, (3) a technically flawless CT scan with documentation of hepatic injury, (4) absence of other intra-abdominal injuries in the abdominal CT scan, and (5) no more than four liver-related blood transfusions. If any one of these criteria is not met, alternative measures should be considered immediately (*Fig. 4*). Neurological integrity has been mentioned as a requirement for the safe non-surgical management of blunt liver injury. The authors believe that, by itself, neurological integrity need not be an absolute requirement for conservative treatment as long as the patient is haemodynamically stable.

Conclusion

In haemodynamically stable patients with blunt hepatic injury, an expeditious abdominal CT scan and a proper classification using the AAST Organ Injury Scale[30] will facilitate non-operative management and the development of protocols. Based on this contemporary review and personal experience, the authors' current treatment philosophy in patients with blunt hepatic trauma includes the following tenets: (1) haemodynamic stability rather than findings on CT determines which patients should be managed conservatively, (2) in haemodynamically stable patients less treatment is probably the best treatment, (3) most blunt hepatic injuries can be managed without operation with minimal morbidity and mortality rates, (4) increasing transfusion requirements should be regarded with suspicion, (5) the interventional radiologist should be part of the treatment team, (6) when conservative management fails, abbreviated laparotomy and planned reoperation should be considered at an early point during surgery, and (7) most complications should be managed in a non-operative fashion unless clear surgical indications are present.

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Review

Early colorectal cancer: recognition, classification and treatment

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Background With the introduction of colorectal cancer screening and improvements in endoscopic technology, the recognition and management of early colorectal cancer assumes increasing importance.

Methods A literature review was undertaken using Medline (National Library of Medicine, Washington DC, USA) searches of the headings early colonic, colorectal and rectal cancer, carcinoma and adenocarcinoma up to and including 1997. All relevant references were examined.

Results and conclusion The diagnosis, classification and treatment options are described. Accurate diagnosis, preoperative and histopathological staging is crucial in the management of early colorectal cancer.

Some 10 per cent of all patients with colorectal cancer have Dukes A tumours[1] and, although about 90 per cent will be cured by surgery, 10–20 per cent go on to develop recurrent disease[2,3]. As the operative mortality rate for elective surgery of this disease is less than 10 per cent and adjuvant treatment is yet to have a substantial impact, early diagnosis offers the only hope at present for improved survival.

The number of early colorectal cancers discovered will increase as screening is introduced; the proportion of Dukes A colorectal cancers may rise to 53 per cent[4]. Two recently published randomized controlled trials of faecal occult blood screening reported increased proportions of Dukes A tumours to 22 per cent[5] and 20 per cent[6]. In a recent Japanese study 75 per cent of asymptomatic cancers were T_{is} (this term, which is not used in Europe, is discussed below) and 22 per cent were T_1 (*Table 1*)[7]. Early colorectal cancer is defined as invasive tumour limited to the mucosa or submucosa. While this can be classified as Dukes stage A, this Dukes category also includes all tumours confined to the bowel wall; to provide better information on the pattern and prognosis of the disease a number of newer staging methods and systems have been developed. Many have been introduced in Japan and are either not known or neglected in European studies. A better definition of local invasion and the probability of lymph node metastasis is essential for the proper use of curative local excision techniques.

Table 1 Tumour staging of colorectal cancer using the tumour node metastasis staging system[14]

Stage	Description
T_X	Primary tumour cannot be assessed
T_0	No evidence of primary tumour
T_{is}	Carcinoma *in situ*: intraepithelial or invasion of the lamina propria
T_1	Tumour invades the submucosa
T_2	Tumour invades the muscularis propria
T_3	Tumour invades through the muscularis propria into the subserosa, or into the non-peritonealized pericolic or perirectal tissues
T_4	Tumour directly invades other organs or structures and/or perforates the visceral peritoneum

T, tumour

Macroscopic classifications

Morphology

Early colorectal cancer presents in many forms and a macroscopic classification has been proposed which is similar to that for early gastric cancer (*Fig. 1*)[8]. The highest proportion of lesions occurs in the rectum and the lowest in the right colon[9,10], but this may reflect the increased use of flexible sigmoidoscopy in Japanese screening programmes[10].

Polyps have been divided into sessile and pedunculated according to their shape, with 42–85 per cent of early colorectal cancers pedunculated and 15–58 per cent sessile[8,10,11]. Patients with pedunculated polyps are less likely to have invasion into the deep submucosal layer[10] (see below). Maruyama classified lesions in the colon according to morphology[13], sessile or polypoid, and according to the length of stalk (*Table 2*); this has been developed further and related to the type of tumour likely to be found within the lesion (*Table 3*)[13]. All lesions of 6–15 mm in diameter fall into the following four types (a–d). For lesions of 6–9 mm in diameter, type a (long stalk) occur mostly in the right colon, type b (short stalk or sessile) have no anatomical predilection, type c (plaque-like) occur in the proximal and descending colon in 30 per cent of cases, and type d (central depression) are all malignant.

Microscopic classifications

The depth of invasion of colorectal cancers has been staged using Dukes classification since 1932. More recently the tumour node metastasis (TNM) classification has become increasingly popular (*Table 1*)[14].

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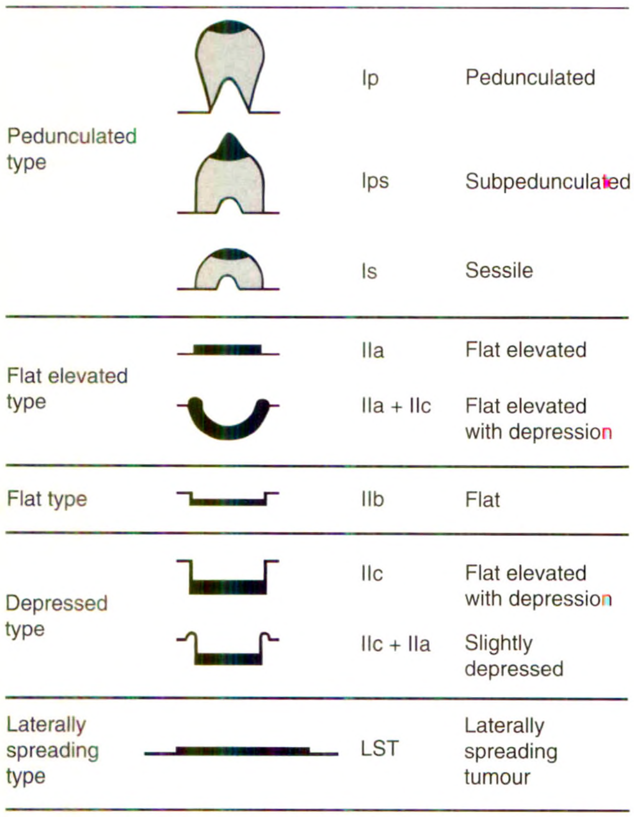


Fig. 1 Macroscopic classification of early colorectal cancer according to Kudo[30]

Table 2 Maruyama classification of the morphology of colorectal lesions[13]

Type	Description
a	Lesion with a long stalk
b	Lesion with a short stalk or a sessile lesion
c	Plaque-like lesion
d	Lesion with a central depression
e	Other

Table 3 Likelihood of cancer within each Maruyama group[13]

Type	Description
a	Benign or early colorectal cancer
b or c greater than 1 cm in diameter with indentation of the colonic wall	Great probability of being early colorectal carcinoma
d with slight depression	Benign or early colorectal cancer
d with severe depression	Benign or early colorectal cancer
e	Mostly villous tumours

Mucosal carcinoma

Europeans are reluctant to use the term carcinoma *in situ* and do not accept intramucosal carcinoma. The Japanese, however, have studied the pattern of growth of colorectal cancer within the mucosa and have subdivided it into intramucosal polypoid growth and intramucosal non-polypoid growth[15]. In one group of 337 polyps, 98 (29 per cent) were early colorectal cancers of which 81 were described as mucosal and 17 as submucosal[16]. While molecular biological techniques may help to identify the earliest stages of malignant transformation from severe dysplasia, at present there is insufficient evidence to support the use of the term 'intramucosal carcinoma'.

Submucosal invasion

Submucosal invasion was described by Haggitt and colleagues[17], who classified early colorectal polyp cancers into pedunculated and sessile types (*Fig. 2*). While this classification has been used widely to assess adequacy of excision in colonoscopic polypectomy specimens, it is less useful for flat lesions without a stalk. The Japanese have several classifications for invasion of the submucosa, including both vertical invasion and horizontal invasion (*Tables 4* and *5*)[10,17], which can be applied more readily to large flat lesions. The former divides the submucosa into upper (Sm1), middle (Sm2) and lower (Sm3) thirds, with some groups attempting to apply measurements within the divisions into thirds[10]. This divides the upper Sm1 layer horizontally according to the thickness of the invasive component of the tumour (*Fig. 3*). In patients with pedunculated polyps, Sm1 is similar to Haggitt level 1, Sm2 is similar to levels 2 and 3, and Sm3 is similar to level 4[10] (*Figs 2* and *3*).

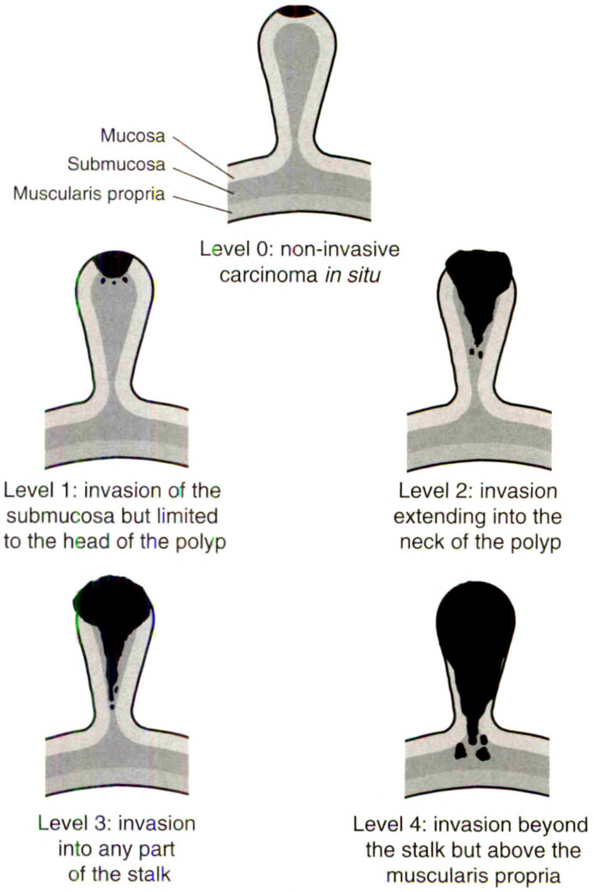

Mucosa
Submucosa
Muscularis propria
Level 0: non-invasive carcinoma *in situ*
Level 1: invasion of the submucosa but limited to the head of the polyp
Level 2: invasion extending into the neck of the polyp
Level 3: invasion into any part of the stalk
Level 4: invasion beyond the stalk but above the muscularis propria

Fig. 2 Classification of early colorectal cancer in polyps according to Haggitt *et al.*[17]

Table 4 Vertical invasion of the submucosa[3]

Class	Description	Kikuchi definition
Sm1	Infiltration into the upper third of the submucosal layer	Invasion from the muscularis mucosa to a depth of 200–300 μm
Sm2	Infiltration into the middle third of the submucosal layer	Intermediate invasion
Sm3	Infiltration into the lower third of the submucosal layer	Invasion near the inner surface of the muscularis propria

Table 5 Horizontal invasion of the upper third of the submucosa (Sm1)

Class	Description
Sm1a	Horizontal invasion limited to less than one-quarter of the width of the tumoral component in the mucosa
Sm1b	Horizontal invasion limited to one-quarter to one-half of the width of the tumoral component in the mucosa
Sm1c	Horizontal invasion greater than one-half of the width of the tumoral component in the mucosa

Adenoma and early colorectal cancer

Early colorectal cancer seems to have two patterns of progression: relatively slow development of cancer in an adenoma, as demonstrated by the adenoma eventually becoming cancerous[18], and a more controversial rapid deep cancerous invasion, as demonstrated by minute flat lesions (type IIb or IIa) arising *de novo*. The proportion of cancers with persisting adenoma decreases with increasing invasion: 74 per cent in mucosal cancer, 33 per cent in submucosal cancer and 0 per cent in cancer with invasion to the proper muscle layer (muscularis propria)[19]. The 'flat' adenomas are more likely to be present with adenoma[12]. It has therefore been proposed that early colorectal cancer loses a component of adenoma in the process of developing into a cancer as it invades the proper muscle layer.

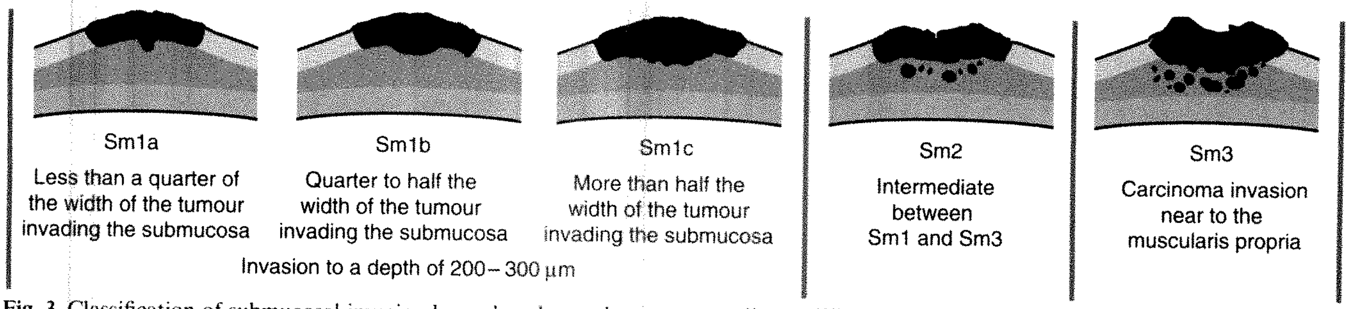
In a study of over 5000 adenomas resected from 24 patients with familial adenomatous polyposis, 18·3 per cent were flat, 12 per cent depressed and 69·7 per cent polypoid[20]. Flat adenomas (types IIb and IIc) were first described by Muto *et al.*[21] and are said to have an overall malignancy rate higher than that of small polypoid adenomas[22–24]. There is no relationship between site and malignancy, but flat adenomas are situated more proximally than 'ordinary' ones[21,23]. The presence of a central depression in a flat adenoma is a sign of increased dysplasia[22,25,26] and it has been suggested that this may be used to determine the degree of malignancy of a lesion at endoscopy. Early cancers with high malignant potential have a slight depression associated with redness on the mucosal surface; carcinomas with high malignant potential have a superficial, minute, irregularly grooved structure or irregular shape with a slight depression on the mucosal surface[27]. The above notwithstanding, flat adenomas may not be precursors of cancer[28].

Diagnosis of early colorectal carcinoma

Detection of flat and depressed types of early colorectal carcinoma during colonoscopy requires awareness of the various macroscopic appearances (*Fig. 1*) and of the fact that there is no elevation above the mucosal surface to facilitate the diagnosis. The incidence of submucosal cancer is higher in early colorectal cancer with depression (IIc, IIc + IIa and IIa + IIc) than in that without depression or in the elevated type (Ip, Isp and Is)[29]. Superficial granularity and nodularity on elevated lesions assists in making the diagnosis of submucosal invasion, and these features on the depressed area of the lesion also suggest submucosal invasion (*Table 6*). Early colorectal cancer is easily overlooked at endoscopy and clues to detection include any irregularity of the mucosal surface, such as pinkishness of the mucosa, fading of the mucosal colour, minute depressions and/or haemorrhagic spots. If an irregularity is observed, dye spraying may make the lesion easier to visualize[30], revealing the innominate (fine) grooves that run circumferentially around the normal colonic surface[31] (some have likened these to the gyri of the brain). These grooves disappear in neoplastic lesions, but remain visible in non-neoplastic lesions and in normal colonic mucosa[32,33].

Another helpful technique is air transformation. When air is insufflated and the colon is observed during distension, the discovery of flat and depressed types is made easier. The depressed part may be emphasized by decreasing the air pressure, as the margins become elevated and the central excavation becomes more prominent; with maximal distension the lesion becomes flat[30].

Magnifying fibre-colonoscopy and dissecting microscopy[34] have been used to study pit patterns in the colon, and modern developments in fibreoptics now allow 100 times magnification *in vivo* during conventional colonoscopy[35]. In the normal and abnormal colorectal


Sm1a
Less than a quarter of the width of the tumour invading the submucosa

Sm1b
Quarter to half the width of the tumour invading the submucosa

Sm1c
More than half the width of the tumour invading the submucosa

Invasion to a depth of 200–300 μm

Sm2
Intermediate between Sm1 and Sm3

Sm3
Carcinoma invasion near to the muscularis propria

Fig. 3 Classification of submucosal invasion by early colorectal cancer according to Kikuchi *et al.*[10]

Table 6 Endoscopic features suggesting submucosal invasion

Depression
Superficial granularity and nodularity
Irregularity of mucosal surface
Fading of mucosal colour
Haemorrhagic spots

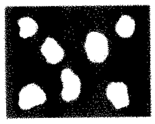
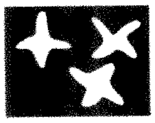
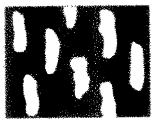
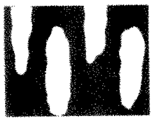
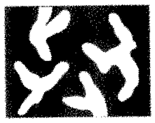
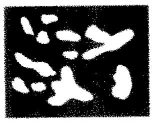
Type	Pit pattern	Definition	Usual histopathological findings
Type I		Round pits	Normal
Type II		Asteroid or papillary pits	Hyperplastic
Type IIIs		Small tubular	Intramucosa adenocarcinoma or depressed adenoma
Type III1		Large tubular or roundish pits	Protruded adenoma
Type IV		Branch or gyrus-like pits	Adenoma or intramuscular adenocarcinoma
Type V		Non-structured pits	Submucosal adenocarcinoma

Fig. 4 Classification of the pit pattern in the colorectal mucosa[30]

mucosa there are five types of pit pattern (*Fig. 4*) which may assist in the diagnosis of early colorectal cancer, as types IIIs and V are found in flat and depressed lesions. Pit patterns have been shown to correspond well with histopathological findings[30].

Use of the high-resolution colonoscope in conjunction with indigo carmine dye has helped in the diagnosis of diminutive colorectal polyps by further aiding the study of pit patterns. Hyperplastic polyps have a characteristic pit pattern of orderly arranged 'dots', resembling normal mucosa, whereas adenomatous polyps have innominate grooves. It has been claimed that the sensitivity and specificity of this technique in distinguishing adenomatous from non-adenomatous colorectal polyps are 93 and 95 per cent respectively[36].

The endoscopic findings associated with adenoma and sessile early colorectal cancer with submucosal involvement are distinguishable by the loss of symmetry, depression or flat surface[37]. One study assessed the diagnostic criteria for early colorectal cancer and compared the radiographic and endoscopic diagnosis based on 157 foci of early cancer[38]. Early cancers were missed by both methods, but radiography missed almost twice as many cancers as endoscopy. It was proposed that both examinations should be carried out if at all possible and that endoscopy should precede radiology to reduce the number of radiologically missed lesions to a minimum. Using such guidelines, 91 per cent of sessile early colorectal cancers may be detected.

Lymph node metastasis and early colorectal cancer

The incidence of lymph node metastasis varies from 0 to 15·4 per cent in early colorectal cancer[10,11,39–49]. The presence of lymph node metastases cannot be determined accurately without colectomy, but several groups have tried to define the risk factors for such metastasis (*Table 7*). The size of the tumour may not be relevant[10,11], but this is disputed by some[50]. Features that may be associated with the presence of lymph node metastasis include 'tumour budding', in which small clusters of undifferentiated cancer cells occur ahead of the invasive front of the lesion[52], the pattern of cancer growth in the submucosal invasive front, tumour differentiation at the leading edge of the lesion, sessile configuration of the lesion, location of the cancer in the rectum[10], and cancer cells in the lymphatics and vessels[16,44,53]. The Japanese Research Society for Cancer of the Colon and Rectum has classified the degree of lymphovascular invasion: ly0 or v0 represents respectively no lymphatic or no vascular invasion, ly1 or v1 signifies very slight invasion, ly2 or v2 denotes moderate invasion, and ly3 or v3 indicates massive invasion[54].

Hase and colleagues[12] examined five histological risk factors for lymph node metastasis in early colorectal cancer (*Table 8*) and found that patients with fewer than four risk factors had no nodal metastases, whereas those with four or five factors had nodal metastasis rates of 33·3 and 66·7 per cent respectively. Occasionally only the deepest part of the tumour contains nests of anaplastic cells that invade the fibrous tissue or vasculature. This focally undifferentiated component probably plays a role

Table 7 Histopathological features and risk of lymph node metastasis[41]

Low risk	High risk
Adenocarcinoma and mucinous adenocarcinoma, well or moderately differentiated	Poorly differentiated adenocarcinoma and mucinous adenocarcinoma
	Signet-ring cell carcinoma
	Undifferentiated carcinoma
	Adenocarcinoma, well or moderately differentiated, containing a focus of any of the above
	Vascular invasion (lymphatic or venous)
	Carcinoma at the resection margins

in the biological evolution of the lesion. One review of the literature in 1989 noted that all patients with lymph node or distant metastases had poorly differentiated carcinomas or tumours with a focus of poorly differentiated carcinoma[41]. It seems important, therefore, for the histopathologist to identify any anaplastic component in an early colorectal cancer as this correlates with the risk of lymph node metastasis.

Considering the intramucosal carcinoma recognized by the Japanese, of 132 patients studied by one group 86·4 per cent had the polypoid growth type, which carried a low incidence (10·2 per cent) of submucosal invasion and minute or scattered invasion into the submucosa. Of the 13·6 per cent of adenocarcinomas that were of the non-polypoid growth type, all had massive invasion with a high frequency of submucosal intralymphatic and venous invasion (72·2 per cent). Non-polypoid growth was not found to be associated with adenoma and so the authors postulated that this type of lesion probably developed *de novo* into the so-called cancer. Interestingly, all of their cases of advanced colorectal cancer were of the non-polypoid type[14].

Lymph nodes containing tumour from early colorectal cancer may well be small, 2–6 mm in diameter in 50 per cent of positive lymph nodes in one series[55]. Others have found that the proportion of positive lymph nodes increases with increasing size of the tumour[50]. Approximately half the patients with lymph node metastases from early colorectal cancer have foci of poorly differentiated tumour, and lymphatic invasion is present in about one-quarter. Distant metastases to the liver and lung have been found with early invasive colorectal cancer, but all have been associated with a primary tumour in the rectum, a sessile type configuration, Sm3 level of invasion and positive lymphatic invasion.

Recurrence of early colorectal cancer

The recurrence rate of early colorectal cancer is between 6·3 and 8·9 per cent[11], but in the presence of lymph node metastases this increases to 36·4 per cent[11,39,44]. The recurrence rate also depends on the type of initial resection performed and this is discussed below.

Treatment

The treatment of flat or depressed types of early colorectal cancer has until recently consisted of either endoscopic removal or surgery. Endoscopic removal includes standard and advanced polypectomy (the injection submucosally of a saline cushion before snaring[56]) which are suitable for small cancers, particularly those that are pedunculated, with further treatment depending on histological findings. Lesions less than 3 cm in diameter should be resected by advanced polypectomy, which can be considered as definitive treatment for intramucosal cancer.

Table 8 Histological risk factors for lymph node metastasis according to Hase *et al.*[12]

Tumour budding
Poor demarcation of cancer at the invasive front
Moderately and poorly differentiated tumour in the submucosal invasive front
Increasing depth of submucosal invasion
Lymphatic invasion

Lesions with discrete infiltration of the submucosa (Sm1a and Sm1b without vessel invasion) may also be suitable for advanced polypectomy. Sm1b with vessel invasion and beyond carries an increased risk of lymph node metastasis and so classical surgical treatment (such as anterior resection) is necessary. Spread to lymph nodes occurs in Sm1b with vessel invasion, but Kudo[30] found no instance of lymph node involvement in the presence of Sm1a or Sm1b without vessel invasion or intralymphatic tumour.

Radical surgery has been proposed for early colorectal cancer with depression (IIa, IIc and IIa + IIc) and for lesions greater than 10 mm in diameter; the latter are cancers that massively invade the submucosal layer (Sm2 and Sm3). *Table 9* outlines Kudo's advice for the treatment of early colorectal cancer[30]. This can be summarized as standard or advanced polypectomy for all tumours other than those with central depression and raised edges (IIa, IIc and IIa + IIc), which should be treated by radical surgery. However, for all types of early colorectal cancer suspected macroscopically to be associated with massive submucosal invasion, surgery alone is preferred to endoscopic treatment, be this transanal endoscopic microsurgery if the pathological tumour stage is pT_1 or possibly pT_2, or more radical surgery if invasion is beyond this. Indications for radical open surgery after polypectomy include cancer at the margin of the polypectomy[42], lymphatic invasion[16] and inadequate tissue for accurate histological assessment[57].

A recent paper has proposed clinical guidelines for the treatment of early colorectal cancer[10], advising that, if the level of invasion is Sm1, cure can be obtained with local resection or endoscopic polypectomy, regardless of other risk factors. If the level of invasion is Sm2 and the lesion is pedunculated or subpedunculated, endoscopic polypectomy or local resection should be performed initially. Patients with no carcinoma at the margins may be followed without additional surgical treatment, but when the margins are not clear classical bowel resection is advised. If the Sm2 lesion is sessile or the lesion is Sm3, classical resection is necessary, especially if there is lymphovascular invasion or the lesion is located in the rectum. Local excision of rectal lesions by a simple transanal approach or the Yorke–Mason procedure has been complemented by the technique of transanal endoscopic microsurgery. This is suitable for tumours between 6 and 20 cm from the anal verge[57]. For pT_1

Table 9 Treatment advocated by Kudo[30]

Lesion	Treatment
Intramucosal carcinoma	Advanced polypectomy
Minute IIc	Advanced polypectomy
IIb ≥ 5 mm in diameter	Advanced polypectomy*
IIc + IIa and IIa + IIc > 10 mm in diameter	Radical surgery
IIa, Ip, Ips, LST < 3 cm in diameter	Standard or advanced polypectomy

*Rarely has submucosal invasion. LST, laterally spreading tumour; see *Fig. 1* for descriptions of other lesions

lesions excised in this way 5-year survival rates of 47–100 per cent have been reported, with low operative morbidity and mortality rates[58–64]. The 5-year survival rate following local excision is probably better than that with polypectomy for pT_1 tumours (100 *versus* 92 per cent)[65]. Transanal endoscopic microsurgery is associated with a lower recurrence rate than simple transanal excision (4·2–10 *versus* 23 per cent)[58,65–68].

Prognosis

Moreaux and Catala[69] found that the overall 5-year survival rate for patients with colorectal cancer limited to the mucosa or submucosa is 97·6 per cent; the 5-year survival rate with positive lymph nodes associated with an early rectal lesion is 56 per cent and if the lesion is in the colon the rate is 73 per cent. Prognostic indicators are depth of tumour invasion, adverse histopathological type (*Table 6*) and lymph node metastasis. Nodal involvement is associated with a poorer prognosis, with 36 per cent of node-positive patients developing cancer recurrence compared with only 6 per cent of node-negative patients ($P < 0{\cdot}005$). Cumulative survival rate is 73 per cent in node-positive patients, compared with 91 per cent in node-negative patients[11]. Clearly it is vital to identify and to treat adequately patients who have lymph node metastasis.

It would be useful to be able to identify early tumours that are likely to recur, and relevant markers are being sought. Recently *p53* gene nuclear overexpression was shown to be unhelpful as an independent prognostic marker for early colorectal cancer[70]. *MUC* genes, which code for the protein component of epithelial mucins, have been studied and a relationship between *MUC2* and the pathogenesis of certain types of colorectal cancer has been suggested[71]. Several phenotypic patterns have been shown to be more prominent in carcinoma, and others in adenoma. There is an association between peritumoral lymphocytic infiltration and $MUC2^-/MUC1^+$ cancers[72]. Markers may help to determine early cancers at high risk of metastasizing and so aid in planning treatment.

Conclusions

Increasing numbers of early colorectal cancers are being identified by screening and heightened awareness in an ever rising elderly population. This requires a careful consideration of the balance between risk of recurrence and morbidity of treatment. The Japanese have proposed several new classifications which seem at first confusing and which need to be applied and assessed in Western populations, especially the prognostic value of the division of the submucosa into three levels. Simplified versions of such classifications may prove useful in evaluating the results of local excision and provide accurate comparisons between treatment protocols.

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Annales de Chirurgie

Digest

Dr Denis Castaing, Editor of *Annales de Chirurgie*, chooses the best from issues six and seven of 1997. A reciprocal digest written by our European Editor, Mr Colin Johnson, is published in the French journal.

Lower limb varicose veins

Good treatment of lower limb varicose veins constitutes a challenge for many surgeons. An important part of number 7 of *Annales de Chirurgie* was dedicated to this old surgical problem.

As reported by Pocard[1] varicose veins of the lower limbs have been described since antiquity in Assyro-Babylonian and Egyptian texts such as the Ebers papyrus, dating from about 1550 BC. Plutarc reported the first varicosectomy which was performed on the Roman general Caïus Marius in 105 BC. The French surgeon of the Middle Ages, Guy de Chauliac, described, in *Chirurgica Magna*, dating from 1350, bandaging for ulcers and cautery or surgical resection for varicose veins. The most remarkable texts were those of Ambroise Paré in the 16th century, using all these techniques for surgical teaching while abandoning many medical treatments based on concepts of disease such as imbalances of 'humours'. The end of the 19th century was the start of a new surgical era with Trendelenburg, Delbert, Mocquot and Mayo, and the development of sclerotherapy, by Pravaz at Wien in 1851.

The second paper by Gillot[2] reported an anatomical study of superficial veins with a calibre of at least 2 mm in 123 limbs (108 normal and 15 with frank varicose disease). The initial network is defined embryologically and subsequent haemodynamic phenomena model the final veins. In particular, the topography of the main perforating veins is relatively fixed. Because of their double antihypertensive valve and aspirating pump function during walking, these vessels drain into saphenous veins. They are beneficial when they return reflux into the deep vessels. Conversely, perforator incompetence contaminates the superficial network as a result of deep reflux. The perforating vessels have a relatively fixed position in relation to the main saphenous collateral veins, their duplicated branches, their communicating veins and the main valves. This results in large junctions typically associating a saphenous valve, one or several collateral veins, one or several communicating veins, and one or several perforating veins. Typical examples are the garter junction for the long saphenous vein and the junction of the tip of the calf for the short saphenous vein. Other haemodynamic levels are situated at various sites, particularly in the leg, reflecting the existence, in some cases, of symmetrical medial and lateral perforating veins. Morphological analysis of 15 limbs with obvious varicose veins of the trunk of the long saphenous vein defined the routes of transmission of reflux to the leg. Finally, the author presents several technical considerations for Doppler operators and surgeons.

The preoperative assessment of varicose veins, which usually requires the use of ultrasonographic methods to specify and localize the various sources of reflux in the saphenous junctions, perforating veins and saphenous branches, was described in the third paper from Baud and Lemasle[3]. Continuous-wave Doppler is the basic technique and duplex scanning provides morphological analysis of the veins and monitors the direction of flow in a precise site. It is particularly useful to study the saphenous junction, perforating veins and deep veins. Colour Doppler imaging offers the advantages of duplex scanning, with visualization of large volumes with blue or red colour-coding according to the direction of flow. All haemodynamic and morphological findings must be reported on a diagram to establish a map of pathological veins.

For a long time, high ligation and stripping of the saphenous trunk was the only technique used to deal with primary varicose veins when surgical treatment was recommended[4]. As duplex ultrasonography has demonstrated that this approach is not effective in many cases, alternative techniques have been proposed and performed. Some of them have not been submitted to randomized and prospective studies. Others, particularly high ligation and stab avulsion of collaterals with preservation of the long saphenous trunk, have been evaluated. The author indicates in which cases high ligation and stripping of the saphenous trunk remains justified and in which situations it is not. All indications must be based on clinical examination and duplex ultrasonography. However, stripping of varicose veins causes pain after operation and sometimes dysaesthesia due to saphenous nerve damage. Ankle wound healing is sometimes painful and often unsightly. Invaginated stripping eliminates some of the drawbacks, but still requires the lower wound and the vein must be left in the case of repeated saphenous rupture. Those two techniques do not allow total saphenous resection in the case of infected ulcers. Constantin *et al.*[5] reported a series of 6157 limbs (3255 patients) operated on by cryosurgery which allows a complete invaginated stripping without an ankle wound. The indication was functional or aesthetic in 5412 cases (88 per cent) and dermitis of hypoderm trophic disorders in 442 cases (7 per cent); 168 limbs (3 per cent) had ulceration and 135 (2 per cent) had superficial venous thrombosis. After operation, one case of sural phlebitis was observed. Fourteen patients had an inguinal wound suppuration. The frequency and intensity of pain and haematomas were decreased. Some 150 of the 168 ulcers were healed after 3 months. The authors concluded that cryosurgery for varicose veins can be used in any circumstances; the lower incision can be avoided thus giving better aesthetic results and cryosurgery has a similar efficacy to the stripping technique.

Ambulatory conservative haemodynamic correction of venous insufficiency is a surgical treatment of superficial venous insufficiency designed to correct the pathological haemodynamic effects of superficial venous insufficiency apparent on standing[6]. This treatment is based on precise preoperative anatomical and haemodynamic mapping performed by duplex ultrasonography, providing preoperative ultrasonographically guided marking. Surgical treatment consists of dividing the hydrostatic pressure column and disconnecting venovenous shunts by ligation–section of the superficial venous network at precise points determined by the preoperative ultrasonographically guided marking. This strategy should achieve a superficial venous circuit draining perfectly into the competent deep venous network. The operation is performed under local anaesthesia as an outpatient procedure and allows immediate resumption of walking, which promotes a good result because of activation of the calf muscle pump. The self-assessment results at 3 years were very good or good in 238 (68 per cent) of 350 in functional terms and 210 (60 per cent) of 350 in aesthetic terms. The authors' conclusions were that this technique is very good provided that reliable preoperative ultrasonographically guided marking and a precise surgical procedure are performed, and that failures are due to poor haemodynamic assessment or inappropriate surgical procedure.

A prospective study of the results of 897 consecutive ambulatory phlebectomies, according to the technique described by Muller in 1966, was reported by Dortu and Constancias-Dortu[7]. Inclusion criteria in this study were based on clinical findings and pulsed Doppler ultrasonography. Patients were reviewed after 1 month and 6 months, then annually. The actuarial rates of good results were 99 per cent at 1 year, 97 per cent at 3 years and 90 per cent at 5 years. In conclusion, the authors recommended that ambulatory phlebectomy has traditional indications (non-saphenous varicose veins, varicose veins of the foot, external pudendal varicose veins) and that ambulatory phlebectomy can also be used as treatment for saphenous varicose veins when the saphenofemoral junction is competent or absent or when the saphenous termination is simple.

Sclerotherapy section consists of a combination of ligations, with section and injection of the proximal and distal segment of the long saphenous vein. This technique is performed under local anaesthesia, 10 cm from the saphenofemoral junction and can be performed as an outpatient procedure. A prospective study of 75 patients (78 limbs operated on, 72 reviewed after 1 year and 65 after 3 years) was reported by Vin *et al.*[8]. Inclusion criteria in this study were incompetent long saphenous vein diameter over 9 mm in older patients whose duplex examination eliminated other leaking points such as anterior or posterior tributaries or the junction, and reflux coming from superficial iliac circumflex veins or from vulvopudendal varicose veins. Sixty-six (92 per cent) of 72 limbs were incompressible without flow or reflux at the saphenofemoral junction level after 1 year and 59 (91 per cent) of 65 limbs after 3 years. Sclerosis with incompressibility without flow or reflux was observed in the lower third of the thigh in 51 (71 per cent) of the 72 limbs after 1 year and in 40 (61 per cent) of the 65 limbs after 3 years, without any clinically detectable underlying varicose recurrence. This technique can be done as an ambulatory procedure and ensures control of saphenofemoral junction reflux. In the majority of reflux cases, the reflux observed in the lower third of the thigh is related to a perforating vein that can feed an underlying varicose network. They were treated by ultrasonographically guided ossifying injection. The authors concluded that the indications for this technique are incompetence of the saphenofemoral junction in older patients with trophic disorders, allowing effective treatment of the source of the reflux with rapid healing of underlying trophic disorders.

Laparoscopic surgery

A series of 98 laparoscopic fundoplications, including seven (7 per cent) for recurrent gastro-oesophageal reflux were reported by Champault *et al.*[9]. Six of these cases occurred within 12 months of surgery. Four were treated successfully by a second laparoscopic procedure. The mean interval between the initial and corrective operation was 10 months. Factors related to failure were technical error, operative inexperience, obesity and the size of the hiatus hernia. Laparoscopic reoperation was relatively straightforward and there were no deaths, but there was an increased risk of pleural effusion. The mean length of hospital stay for reoperations was identical to that of initial operations (4 days). No further recurrences were noted after a mean follow-up of 1 year (range 280–475 days). The authors conclude that early failures following laparoscopic fundoplication can be effectively dealt with by laparoscopic surgery.

A retrospective study was designed by Habib *et al.*[10] to compare the cost of laparoscopic appendicectomy in 114 patients operated on during 1991–1992 and open appendicectomy in 114 patients operated on during 1989–1990. Patients were matched for sex, American Society of Anesthesiologists (ASA) score and age into two homogeneous series. Costs of accommodation, operation and time off work were calculated by the observed costs method to assess daily cost of the inpatient unit, hourly cost of the operating room–recovery ward and the patient's consumption. A mean specific cost was added in the case of laparoscopic appendicectomy. A significant difference was observed in operating time (mean(s.d.) 43(18) min for laparoscopic appendicectomy *versus* 64(28) min for open appendicectomy; $P<0{\cdot}01$), postoperative stay (5·4(4·5) *versus* 4·3(2·2) days; $P<0{\cdot}02$), and time off work (31(10) *versus* 22(7) days; $P<0{\cdot}01$). The mean(s.d.) total cost of the treatment was 26 712(8829) French francs for laparoscopic appendicectomy and 23 040(6365) French francs for open appendicectomy ($P<0{\cdot}01$). The higher cost of the operation in the case of laparoscopic appendicectomy was not compensated by the reduction in accommodation costs. A clinical benefit in terms of reduction of pain and local complications has been reported in the literature. The cost of hospitalization is higher with laparoscopic appendicectomy, but the cost of the time off work is decreased. The conclusion was that laparoscopic appendicectomy provides clinical benefit in all patients and an economic benefit in patients with a professional activity.

From December 1989 to May 1995, a prospective study of laparoscopic cholecystectomy was carried out by Colonval *et al.*[11] to assess the reliability and safety of this method in cases of acute cholecystitis. During this period, 1453 patients underwent laparoscopic cholecystectomy. Acute cholecystitis was diagnosed in 280 patients, based on clinical history and macroscopic lesions. Only 221 patients (15 per cent) were included in the study after positive histology was obtained (86 men; 135 women). The mean age was 62 (range 20–90) years. Sixty-two patients (28 per cent) were classified as ASA III and IV. The mean interval between the first symptoms and operation was 10 (range 1–53) days. The mean operating time was 130 (range 45–420) min. Conversion to an open procedure was necessary in 22 patients (10 per cent). The operative mortality rate was 1 per cent (two patients classified ASA grade IV) and the overall morbidity rate was 13 per cent. A bile duct injury occurred in one patient. The authors conclude that laparoscopic cholecystectomy for acute cholecystitis is a safe procedure, when performed by operators experienced in laparoscopic surgery.

Laparotomy has no benefit in 5–39 per cent of patients suffering from penetrating abdominal trauma[12]. In a prospective study to determine the value of laparoscopy in the management of such patients, 13 patients (11 men; mean age 32 years) underwent laparoscopy for abdominal knife wounds. Two patients had a non-penetrating abdominal wound (one with a pneumothorax and one with a parietal haematoma). Eleven patients had a peritoneal penetrating wound and only four of them had lesions that required surgical treatment (two intestinal wounds, one gastric wound and one coeliac artery disruption). No treatment was required in three patients (one wound of the intestinal serosa and two superficial hepatic wounds). In the remaining six patients no visceral wound was found. There was no death or morbidity. No lesions were missed at laparoscopy and laparoscopy avoided unnecessary laparotomy in nine of 13 patients. The authors suggest that laparoscopy is a reliable method for the management of patients with abdominal wounds, allowing a very sensitive and specific diagnosis of penetration and visceral injuries. In some cases, it allows laparoscopic treatment of the visceral injury.

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Circulating bile is the main factor responsible for atrial natriuretic peptide release in experimental obstructive jaundice

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Background Biliary obstruction in the rabbit causes increased release of atrial natriuretic peptide (ANP). Circulating bile, raised biliary pressure or absence of bile in the duodenum may be implicated in this hepatocardiac syndrome.

Methods An experimental model was developed to elucidate the mechanism linking obstructive jaundice and increased plasma ANP. Hepatic and renal function, biliary tree pressure and ANP plasma concentrations were investigated in conscious rabbits 4 and 24 h after common bile duct ligation, biliovenous shunting or external drainage via a biliary fistula.

Results Bilirubin concentration increased after bile duct ligation and creation of a biliovenous shunt. Plasma creatinine increased abruptly in rabbits with a biliovenous shunt. At 4 h, the ANP increase in animals with a biliovenous shunt was ninefold that observed after bile duct obstruction while no change was noted after external biliary diversion (mean 350 *versus* 45 *versus* 9 fmol/l; $P < 0{\cdot}01$). Relief of biliary tree obstruction was associated with a return of ANP levels towards basal normal values.

Conclusion Raised plasma ANP in obstructive jaundice is not the result of an increased biliary pressure *per se* or absence of bile in the proximal duodenum but of the passage of bile components to the circulation.

Extracellular volume depletion may be an important factor influencing renal function in obstructive jaundice[1,2]. In conscious rabbits with bile duct ligation, volume depletion has been observed to be associated with profound hypodipsia, hypophagia and inappropriate diuresis[3,4]. These derangements of water and sodium metabolism are associated with high plasma concentrations of renin, aldosterone, vasopressin and atrial natriuretic peptide (ANP)[4]. The latter is the result of increased release of this peptide from the heart[4]. Furthermore, increased atrial staining for ANP and increased atrial content of this peptide hormone were noted in jaundiced rabbits when compared with sham-operated controls[5]. While increases in plasma renin and aldosterone are a logical endocrine response to a reduced extracellular water compartment, high plasma concentrations of ANP seem to be a primary non-compensatory abnormal response of atrial cardiocytes to biliary obstruction[4,5].

The mechanism of ANP release in obstructive jaundice is not known. Increased biliary pressure, circulating bilirubin or absence of bile in the duodenum can theoretically all be involved. In the present study, a new experimental model is reported which permits further elucidation of the mechanism of ANP release.

Materials and methods

Animal model

Twenty-two male New Zealand rabbits with weights ranging between 2650 and 3900 (mean 3200) g were kept in individual cages and given free access to water and chow (Panlab, Barcelona, Spain). After 1 week of adaptation they were submitted to a surgical procedure under general anaesthesia induced with subcutaneous Ketolar 100 mg/kg (Parke Davis, Madrid, Spain), Thalamonal 0·5 mg/kg (Syntex Latino, Barcelona, Spain) and atropine 0·5 mg. Catheters were inserted into both jugular veins (*Fig. 1*); the right was used for blood sampling and the left for drainage of bile from the gallbladder (biliovenous shunt). Both jugular catheters were tunnelled to the occipital region where they were secured to the skin with 000 silk sutures. The common bile duct was ligated with 0000 silk close to the duodenum through an upper midline incision. Catheters were placed in the gallbladder and within the duodenal lumen (*Fig. 1*), and then exteriorized and connected to a three-way stopcock. An additional line was eventually connected to catheter B to create a biliovenous shunt. Bile flow was directed through the three-way stopcock either to the duodenum or to catheter D. By occluding catheter C, complete biliary obstruction was produced and by leaving it open complete external biliary diversion was obtained. The laparotomy wound was closed with 000 silk sutures. Cloxacillin 250 mg was administered intravenously at the beginning and end of the operation. After operation the animals were equipped with a jacket (Alice King Chatam, Los Angeles, California, USA) to prevent damage to the catheters.

Experimental protocol

On the fourth day after operation, animals were lightly sedated with diazepam 5 mg/kg and Thalamonal 0·5 mg/kg and randomized into three groups: bile duct obstruction (group CBDL, $n = 8$); biliovenous shunt (group BVS, $n = 8$) and biliary diversion via a external biliary fistula (group BF, $n = 6$). At 0, 5, 10, 15, 20 and 30 min, and 1, 2, 4 and 24 h after biliary obstruction, biliovenous shunting or biliary diversion, biliary pressure was recorded through the left jugular catheter. Blood samples were obtained to determine osmolality and levels of urea, creatinine, sodium, potassium, total bilirubin and alkaline phosphatase (Technicon Instruments, Tarrytown, New York,

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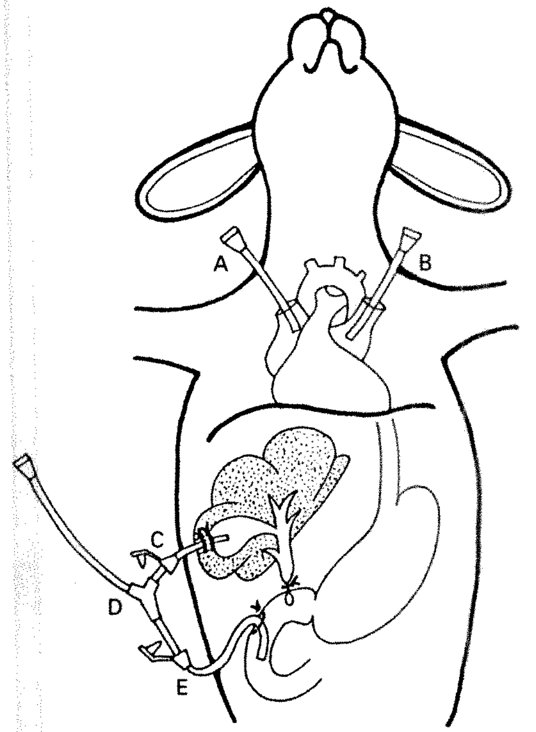

Fig. 1 Physiological preparation for creating complete biliary obstruction, a biliovenous shunt or a biliary fistula. A, right jugular catheter; B, left jugular catheter; C, gallbladder catheter; D, central venous pressure catheter to record biliary pressure; E, duodenal catheter

USA) at time 0, and after 1, 2, 4 and 24 h. ANP was also determined in these blood samples by radioimmunoassay as described previously[3]. A volume of saline similar to that of each blood sample was infused through the catheter to avoid extracellular volume depletion. Also, the bile lost in group BF was replaced with an equal volume of intravenous saline. In group CBDL, the duodenal catheter obstruction was released at the end of the 24-h study period to restore bile flow from the gallbladder to the duodenum. Biliary pressure was recorded again and blood samples were taken at 48 and 72 h for biochemical analysis and ANP measurements. All the animals were killed humanely at the end of the study and a post-mortem examination was carried out to check the patency of the catheters, the absence of mechanical complications and the presence of cholestasis.

Statistical analysis

Results are expressed as mean(s.d.). Intergroup analysis at 4 and at 24 h after biliary tract manipulation was carried out using the factorial analysis of variance test and Snedecor's F-value; and the two-tailed Student's *t* test for paired and unpaired data as required. Data processing was done with a Macintosh II computer (Apple, Cupertino, California, USA) and the Statview II statistical package (Abacus Concepts, Berkeley, California, USA). Statistical significance was set at $P < 0\cdot05$.

Results

Basal metabolic variables (serum electrolytes, renal and liver function tests and ANP levels) were similar in all three experimental groups at the beginning of the study, 4 days after surgical preparation.

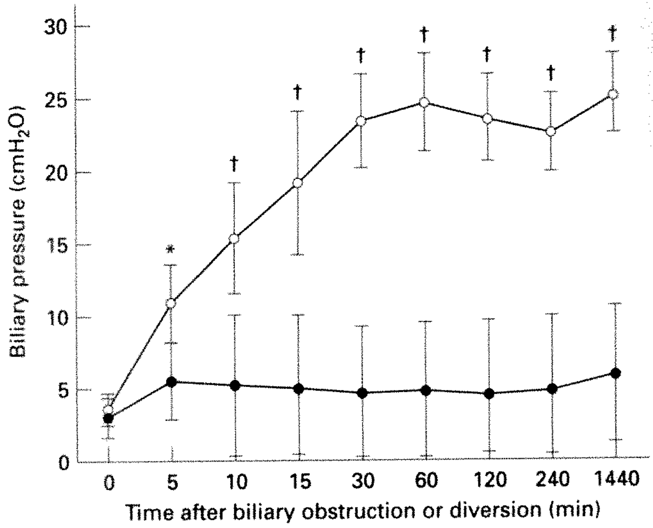

Fig. 2 Mean(s.d.) biliary pressure at time 0 (baseline value) and after common bile duct obstruction (○) and biliovenous bypass (●). $^*P < 0\cdot05$, $^\dagger P < 0\cdot001$ *versus* BVS group (Student's *t* test)

Biliary pressure

After obstruction of the duodenal catheter, the pressure within the biliary tree increased rapidly to attain its maximum value at 1 h (*Fig. 2*). After releasing the obstruction, the pressure returned to its normal baseline value: 4·4(1·3) cmH$_2$O at 48 h and 3·8(1·3) cmH$_2$O at 72 h. In group BVS, biliary pressure did not change and remained around baseline value throughout the study.

Obstructive jaundice

In group CBDL there were significant increases in bilirubin and alkaline phosphatase levels at 4 and 24 h (*Tables 1* and *2*) which returned to normal after restoration of bile flow. In group BVS bilirubin values were significantly higher than those observed in group CBDL but the alkaline phosphatase level remained normal.

Table 1 Liver and renal function 4 h after biliary obstruction, biliary venous diversion or external drainage via a biliary fistula

	Group CBDL ($n=8$)	Group BVS ($n=8$)	Group BF ($n=6$)	P^*
Bilirubin(μmol/l)	11(4)‡	52(37)‡	2(1)	<0·001
Alkaline phosphatase (units/l)	277(132)‡	66(46)	93(10)	<0·01
Urea(mmol/l)	8(5)	10(5)†	7(2)	n.s.
Creatinine(μmol/l)	87(26)	152(71)†	71(18)	<0·05
Sodium(meq/l)	146(14)	129(11)	143(4)	<0·05
Potassium(meq/l)	3·3(0·8)	3·1(0·8)	4·1(0·8)	n.s.
Serum osmolality (mosmol/kg)	311(35)	294(33)	291(4)	n.s.
ANP(fmol/l)	45(37)†	350(168)§	9(3)	<0·001
Biliary pressure (cmH$_2$O)	22·6(2·7)§	4·8(5·2)		<0·001

Values are mean(s.d.). CBDL, common bile duct ligation; BVS, biliovenous shunt; BF, biliary fistula; ANP, atrial natriuretic peptide; n.s., not significant. *Analysis of variance. $^\dagger P < 0\cdot05$, $^\ddagger P < 0\cdot01$, $^\S P < 0\cdot001$ *versus* basal value (Student's paired *t* test)

Table 2 Liver and renal function 24 h after biliary obstruction, biliary venous diversion or external drainage via a biliary fistula

	Group CBDL ($n=8$)	Group BVS ($n=8$)	Group BF ($n=6$)	P*
Bilirubin (μmol/l)	45(9)‡	182(98)‡	2(1)	$<0{\cdot}01$
Alkaline phosphatase (units/l)	389(169)‡	51(46)	96(10)	$<0{\cdot}01$
Urea (mmol/l)	9(5)	30(5)‡	8(3)	$<0{\cdot}001$
Creatinine (μmol/l)	92(31)	431(140)†	88(26)	$<0{\cdot}001$
Sodium (meq/l)	146(20)	130(17)	139(3)	n.s.
Potassium (meq/l)	3·4(0·6)	3·8(0·7)	3·9(1·0)	n.s.
Serum osmolality (mosmol/kg)	311(47)	307(28)	290(6)	n.s.
ANP (fmol/l)	37(17)‡	132(72)§	10(1)	$<0{\cdot}01$
Biliary pressure (cmH$_2$O)	25·3(2·7)§	5·9(4·7)		$<0{\cdot}001$

Values are mean(s.d.). CBDL, common bile duct ligation; BVS, biliovenous shunt; BF, biliary fistula; ANP, atrial natriuretic peptide; n.s., not significant. *Analysis of variance. †$P<0{\cdot}05$, ‡$P<0{\cdot}01$, §$P<0{\cdot}001$ *versus* basal value (Student's paired *t* test)

Renal function

In groups CBDL and BF there were no significant changes in urea concentration and in plasma electrolytes at 4 or 24 h. Urea and creatinine plasma concentrations increased significantly in group BVS, attaining values characteristic of acute renal failure at 24 h.

Atrial natriuretic peptide

After duodenal catheter obstruction in group CBDL, the ANP plasma concentration increased steadily reaching a threefold increase over basal values from 2 to 24 h (*Fig. 3*). After bile flow was re-established, ANP plasma concentrations tended to return to normal, and at 24 and 72 h they were no different from basal values: 19·8(14·4) and 17·7(17·9) fmol/l respectively. In group BVS, ANP concentration showed a ninefold rise 4 h after biliary venous diversion and remained increased throughout the 24-h study period. In group BF, ANP concentration was unchanged.

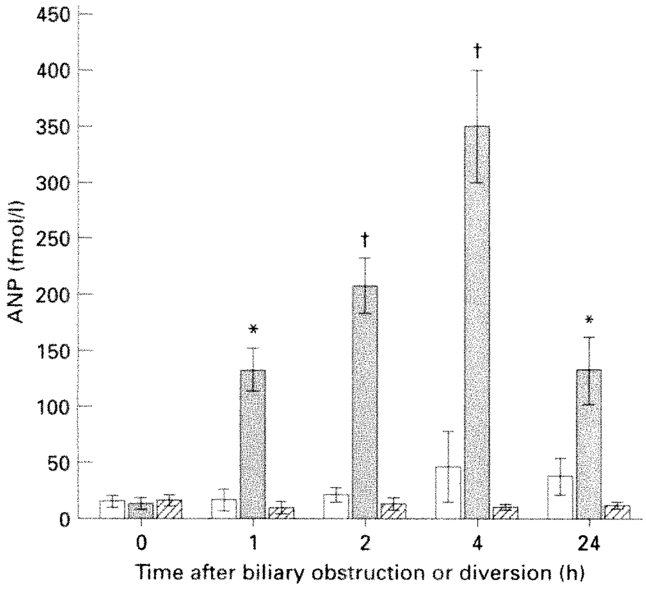

Fig. 3 Mean(s.d.) atrial natriuretic peptide (ANP) plasma concentrations at time 0 (basal value) and after common bile duct obstruction (□), biliovenous bypass (▒) and external drainage via a biliary fistula (▨). *$P<0{\cdot}01$, †$P<0{\cdot}001$ (analysis of variance)

Discussion

The pathogenesis of renal dysfunction associated with obstructive jaundice and acute cholangitis is becoming progressively clarified. Extracellular volume depletion has been reported both in animals and in humans with biliary obstruction[1,2]. In rabbits, plasma volume is reduced by 15 per cent 12 days after common bile duct ligation[1] and this is associated with water and sodium retention[6]. Thus, a reduced extracellular water compartment, with marginal hypovolaemia, appears to be a significant factor predisposing to renal failure, particularly when associated with perioperative haemorrhage, hypotension[7], and administration of diuretics[8] or nephrotoxic drugs[9]. The need for appropriate preoperative hydration of patients undergoing surgery for biliary obstruction has been underlined by Parks *et al.*[10]. These authors compared hydration alone with hydration and dopamine and found no differences in the incidence of postoperative renal dysfunction after these treatments.

In animal models, water and sodium depletion are linked to hypodipsia, hypophagia and inappropriate diuresis and natriuresis[3,11]. Fractional excretion of sodium is increased 4 h after bile duct ligation[12]. The ANP plasma concentration has been found to be raised in rabbits with obstructive jaundice[3–5] and therefore this peptide could be implicated in the loss of the thirst mechanism and sodium appetite, and in the inappropriate natriuresis observed in these animals[3,4]. The rise in ANP plasma concentration has been confirmed in the present study. Furthermore, this increase was found to be reversible, depending on the relief of biliary obstruction. In contrast with these findings, ANP release has not been found to be raised in rats after 2–5 weeks of biliary obstruction[13] (and unpublished results from Vakil *et al.*). In one study, however, ANP messenger RNA was increased in the atria of bile duct ligated rats as well as glomerular ANP receptor density[13]. In the dog, ANP increase has only been detected after 5–6 weeks of jaundice[14]. It has to be taken into account, however, that rats and dogs develop cirrhosis and ascites following bile duct obstruction ('wet models'), while the rabbit and the baboon show a cholestatic syndrome more akin to the human condition ('dry models'). Another factor that could explain differences in ANP plasma concentrations is timing between biliary obstruction and blood sampling. In these studies, ANP was not determined in the early phases of obstructive jaundice.

The cause of raised plasma concentrations of ANP in obstructive jaundice is not known. The level of this hormone has been found to be increased in diseases associated with extracellular volume expansion and atrial distension[15]. Thus, in obstructive jaundice increased ANP concentration appears to be a paradoxical phenomenon since this disease is characterized by hypovolaemia rather than hypervolaemia; therefore, other mechanisms for ANP release should be operative. Increased pressure within the biliary tract and/or the direct action of some bile component on the right atrium were thought to be the two mechanisms possibly linking biliary obstruction to ANP release. Also, recent reports suggest that ANP may be a regulatory gastrointestinal peptide since it has been identified in the upper gastrointestinal tract[16]. According to the results of the present study, however, neither increased biliary pressure *per se* nor the absence of bile salts in the duodenum can be incriminated as a cause of increased plasma ANP concentration. Thus, it appears that the presence of bile components in the blood is essential to the ANP response.

Topuzlu and Stahl[17] found an increased diuresis and natriuresis after direct intravenous infusion of bile. A similar renal response was found by Levy and Finestone in dogs during 4 h of common bile duct obstruction[12]. These authors were able to reproduce the natriuretic response to biliary obstruction in healthy dogs by cross-circulation and postulated the existence of a humoral mechanism. The current study shows that the presence of bile products in the circulation is a very powerful stimulant of ANP release. This peptide could well be the humoral factor postulated by these other investigators.

At present the mechanism whereby bile components release ANP from the heart can only be speculated upon. The presence of bile products in the blood may diminish cardiac contractility and may result in increased ANP synthesis through stretching of the atria. ANP plasma concentrations appear to accurately reflect left ventricular function and seem to be very sensitive to even minimal asymptomatic myocardial dysfunction[18]. In dogs with a choledochocaval shunt, the Haifa group has shown a reduction of the left ventricle contractility[19], although they were unable to detect ultrastructural myocardial damage in this model or in dogs with bile duct ligation[20]. More recently, Jacob *et al.*[21] have reported a decreased myocardial contractility in rats 3 days after common bile duct ligation, independent of changes in the number or responsiveness of beta adrenergic receptors. Direct biliovenous reflux, however, appears to magnify the adverse consequences of biliary obstruction. Reflux results in much higher plasma bilirubin and ANP levels and leads to acute renal failure either through a direct toxic effect of bile components on the renal parenchyma and/or through arteriolar vasoconstriction mediated by prostaglandins[22]. Thus, although bile passes to the venous circulation during biliary obstruction, the liver parenchyma probably acts as a filter by either reducing the hepatic synthesis of biliary products or clearing them before they enter the venous circulation.

In summary, this study shows that ANP is released by the presence of bile components in the plasma and that neither raised biliary tree pressure nor absence of bile salts in the proximal gut can be incriminated as the cause of increased ANP concentration. Decreased myocardial contractility and auricular stretching may be the factors linking circulating bile and increased heart endocrine activity.

Acknowledgements

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Total vascular exclusion of the liver for the resection of lesions in contact with the vena cava or the hepatic veins

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Background This study reviews experience with total vascular exclusion of the liver (TVE), for the resection of tumours in contact with the hepatic veins or the vena cava.

Methods A retrospective study was carried out of 366 hepatic resections performed over 13 years. Forty-one patients (11 per cent) were operated under TVE.

Results Twenty-four patients were operated for malignancy and 17 for benign disease. Major hepatectomy was performed in 26 patients and minor hepatectomy in 15. The technique allowed vascular repair in eight patients. Median intraoperative blood transfusion was 2 (range 0–26) units; 14 patients required none. Median duration of TVE was 29 (range 5–58) min. No deaths occurred. Significant complications occurred in ten patients. Morbidity was related to the malignant nature of the lesion, duration of surgery and volume of blood transfusion, but not to duration of TVE.

Conclusion TVE facilitates resection of critically located hepatic lesions with safety and minimal blood loss. Within the limits of 1 h, prolonged TVE does not increase morbidity.

The limits of hepatic surgery have been extended recently thanks to advances in anaesthesiological management, improved surgical techniques and technologies, and better understanding of the functional anatomy of the liver[1–3]. It has long been recognized that intraoperative bleeding was of foremost importance in the development of perioperative morbidity and death[4–8]. Several methods intended to limit bleeding have been developed with the first description of portal triad clamping by Pringle in 1908[9], which led to the development of total vascular exclusion of the liver (TVE) by Heaney *et al.* in 1966[10]. Since then, Huguet and colleagues[11–13] have better characterized and widely advocated the use of TVE, showing good tolerance of the liver to haemodynamic changes and warm ischaemia. TVE provides control of the hepatocaval connection, and thus allows resection of tumours adjacent to the vena cava and the hepatic veins with limited risk of massive haemorrhage or air embolism, which are the two major hazards in this type of surgery.

Whereas TVE is performed almost routinely in most institutions where it is used[14,15], the present authors use it exclusively for resection of lesions situated in contact with the hepatocaval connection. As few series of hepatectomies under TVE for this type of tumour are available, experience with TVE has been reviewed, with special regard to death and morbidity and their relation to blood loss and duration of liver ischaemia.

Patients and methods

Patients

From February 1984 to February 1997 (13 years), 366 patients underwent liver resection in this institution. For all patients, resectability was assessed by computed tomography, selective coeliomesenteric angiography with late-phase portography and, for some of the more recent cases, magnetic resonance imaging. Fifty-seven patients with lesions situated in close contact with the hepatic veins or the inferior vena cava were considered for resection under TVE. For 14 of these patients, a complete dissection to prepare for TVE was done but TVE was not performed, because it appeared in the process of surgery that safe hepatectomy could be achieved without recourse to it. Occlusion of the vena cava was not performed in two patients, and surgery with additional aortic clamping was necessary in one patient, because of poor haemodynamic tolerance. Thus 41 patients underwent hepatectomy under TVE during this period. Median patient age was 49 (range 20–73) years. There were 22 women and 19 men. Indications for liver resection are shown in *Table 1*. Three patients had evidence of liver cirrhosis, and the other 38 had a non-cirrhotic liver parenchyma. American Society of Anesthesiology (ASA) grade was I or II in all patients but five who were graded ASA III, and one ASA IV.

Relationship of tumours with the hepatocaval confluence

Only patients with lesions in close contact with either element of the hepatocaval confluence were considered for TVE. The tumours involved the vena cava on 21 occasions, the middle hepatic vein 24 times, the right hepatic vein 16 times and the left hepatic vein 11 times. More than one vein was involved in the

Table 1 Indications for liver resection under total vascular exclusion

Indication	No. of patients
Malignancy	
Metastasis	13
Hepatocellular carcinoma	7
Cholangiocarcinoma	4
Total	24
Benign disease	
Focal nodular hyperplasia	7
Haemangioma	6
Hydatid cyst	2
Adenoma	1
Caroli's disease	1
Total	17

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majority of patients. Notably, in three patients the tumour was set anteriorly against the vena cava and in close contact with all three elements of the venous hepatic pedicle. In addition, TVE allowed repair of tears on a hepatic vein in seven patients, and reconstruction of a narrowed, single remaining left hepatic vein in one case.

Operative technique

The surgical technique was that described by Huguet *et al.*[13]. In general a bilateral subcostal incision was used (34 patients) completed in one case with a right thoracotomy. Occasionally, mostly in early cases, a vertical midline incision was performed (seven patients), completed in six patients with a right thoracic extension and in one with a transverse incision. From 1988, intraoperative ultrasonography was performed routinely to determine the exact vascular relationships of the tumour to be removed. All the hepatic ligaments were divided to allow complete mobilization of the liver and exposure of the whole retrohepatic vena cava. TVE was prepared by carefully dissecting the suprahepatic and infrahepatic vena cava, and right adrenal veins and accessory hepatic veins were ligated if necessary to allow complete venous control during clamping. Unless an atypical resection was planned, control of the hilar structures was first performed, with ligation of the portal and arterial elements, after trial clamping to assess discoloration of the parenchyma to be removed. In the interests of safety, biliary tract elements were usually ligated during parenchymal transection. Clamps were always applied in the same sequence: infrahepatic vena cava, portal triad and suprahepatic vena cava. If a left hepatic artery was present, it was controlled by a fourth clamp in order to completely interrupt arterial blood flow to the liver. A trial clamping of 2–5 min was then done, to ascertain haemodynamic tolerance. Clamps were released for a few minutes before proceeding with liver transection, which was done by carefully crushing the liver parenchyma with a Kelly forceps ('kellyclasie'), with ligation of vascular structures greater than 2 mm in diameter and electrocoagulation of the smaller ones. When a long-lasting resection was planned, the first stages of the dissection were performed without vascular exclusion or with single portal triad clamping, in periods no longer than 12 min, with 5–10-min intervals, until TVE was necessary because of the vicinity of the hepatic veins or the vena cava. After completing the resection, the clamps were removed in the reverse order of their application. Haemostasis of the raw surface of the liver was assured by argon beam coagulation and completed by application of a biological fibrin glue (Tisseel/Tissucol, Immuno AG, Vienna, Austria) and sealing with haemostatic material (Tabotamp, Johnson and Johnson, Skipton, UK) and a patch of omentum if available. Closed drainage was established only when a biliary leak could not be ruled out absolutely.

Couinaud's description of the functional anatomy of the liver was used for designation of the segments and definition of hepatectomies[1,16].

Data collection and analysis

All medical records of patients considered for TVE were reviewed retrospectively and demographic, laboratory, intraoperative, histopathological and clinical data were collected.

Significant morbidity was defined as complications of grade II or more according to Clavien *et al.*[17]. Briefly, this applies to patients with life-threatening complications that required surgical or drainage procedures, that caused residual disability or that prolonged hospitalization over twice the median postoperative hospital stay. Perioperative death was defined as that occurring during the hospital stay or up to 30 days after operation if the patient was discharged earlier.

Several variables were compared for their roles in morbidity, intensive care unit stay and postoperative hospital stay. Mann–Whitney *U* test was used for comparison of continuous variables, and χ^2 with Yates' correction or Fisher's exact test for discrete variables when applicable. Correlation was assessed by linear regression and Pearson's coefficient was calculated. $P<0{\cdot}05$ was considered significant.

Results

Types of resection for the 41 patients are shown in *Table 2*. Resections were called major if three segments or more were removed according to Couinaud's classification[16]. Median operating time was 6 h (range 2 h 20 min to 12 h) and median duration of TVE was 29 (range 5–58) min). Intermittent single portal triad clamping was used in the course of resection for 13 patients before undertaking TVE. One or two periods of clamping of 8–15 min were carried out in these patients. Median intraoperative blood transfusion was 2 (range 0–26) units of packed red blood cells, and 14 patients required none.

There was no intraoperative or postoperative death. Twenty-one significant complications occurred in ten patients and are listed in *Table 3*. One patient developed transient severe postoperative liver failure with encephalopathy. Transient moderate hepatocellular failure (prothrombin time less than 50 per cent) without clinical symptoms was observed in 11 additional patients. Renal failure (creatinine level above 125 μmol/l) was observed in one patient with pre-existing moderate chronic renal failure, but the patient's blood creatinine level remained stable. These patients spent a median of 2 (range 0–7) days in the intensive care unit, and were discharged from hospital after a median postoperative stay of 13 (range 7–65) days.

Several risk factors were studied for occurrence of postoperative complications and results of the analysis are shown in *Table 4*. The only significant differences between patients with or without complications were in the malignant nature of the lesion, duration of surgery and volume of blood transfusion. Duration of surgery and amount of blood transfused were not independent variables as they were correlated ($r=0{\cdot}43$, $P<0{\cdot}005$).

Table 2 Type of liver resection performed under total vascular exclusion

Operation	No. of patients
Major resection	
Extended right hepatectomy*	6
Right hepatectomy*	8
Extended left hepatectomy*	4
Left hepatectomy*	8
Total	26
Minor resection	
Left lobectomy*	1
Bisegmentectomy III–IV	1
Bisegmentectomy IV–VIII	1
Segmentectomy VII	1
Segmentectomy IV	1
Tumorectomy	10
Total	15

*In the American literature[16,18], extended right hepatectomy corresponds to right trisegmentectomy (segments IV–VIII with or without segment I), right hepatectomy to right lobectomy (segments V–VIII), extended left hepatectomy to left trisegmentectomy (segments I–IV, with or without segments V, VIII), left hepatectomy to left lobectomy (segments II–IV), and left lobectomy to left lateral segmentectomy (segments II and III)

Table 3 Significant complications in ten patients operated under total vascular exclusion of the liver

Complication	No. of patients
Abdominal	
Biliary leak	3
Ascites	2
Hepatic necrosis*	1
Acute pancreatitis	1
Splenic rupture	1
Small bowel occlusion	1
Thoracic	
Pleural effusion	5
Pulmonary embolism	2
Pericardial effusion	1
Haemothorax	1
Other	
Encephalopathy	1
Sepsis	1
Adrenal failure	1

Several patients had more than one complication. *This patient developed necrosis of segment II after a right trisegmentectomy for hepatocellular carcinoma

Table 4 Risk factors for the development of complications in patients operated under total vascular exclusion of the liver

Risk factor	Patients with complications ($n = 10$)	Patients without complications ($n = 31$)	P
Mean age (years)	51	48	n.s.‡
Sex ratio (M:F)	4:6	15:16	n.s.§
Mean ASA grade	2·0	1·7	n.s.‡
Cirrhosis	1	2	n.s.§
Malignancy	9	15	< 0·05§
Major resection*	7	19	n.s.§
Mean transfusion requirement (units)†	5·2	3·5	< 0·05‡
Mean duration of vascular exclusion (min)	29	32	n.s.‡
Mean duration of operation (h)	8·2	5·4	< 0·01‡

*Three or more segments of Couinaud removed; †units of packed red blood cells transfused at operation. ASA, American Society of Anesthesiologists; n.s., not significant. ‡Mann–Whitney U test; §χ^2 or Fisher's exact test

Duration of vascular exclusion was not found to be a risk factor for complications, nor did it correlate with either intensive care unit stay ($r = 0·1$, $P > 0·5$) or postoperative hospital stay ($r = 0·06$, $P > 0·5$).

Discussion

Advances in the techniques of vascular exclusion of the liver have dramatically improved achievements in the performance of surgery for tumours of the hepatocaval connection. Since clamping of the portal triad alone[9] did not prevent hepatic venous bleeding or air embolism, new ways of vascular exclusion had to be devised. The first techniques described involved cross-clamping of the aorta[10] because of concerns about haemodynamic tolerance, or hypothermic perfusion of the liver[19] because of concerns about tolerance to warm ischaemia. Since then, Huguet and colleagues[20,21] have shown that aortic clamping is seldom necessary, as patients generally adapt well and quickly to the haemodynamic changes observed, and that the hepatocytes can tolerate periods of normothermic ischaemia in excess of 1 h[22]. A modern technique, which is used in this institution, has emerged from this pioneering work and allows resection of lesions in close contact with the vena cava and the hepatic veins with a very limited risk of air embolism or massive haemorrhage. These hazards would have made impossible the safe resection of most of the tumours reported here, if TVE had not been available. In many instances, achievement of a bloodless operative field has allowed close dissection or repair of the hepatic veins or the vena cava and has limited the blood transfusion required in these patients. That 14 of 41 patients in this series did not require blood transfusion is noteworthy, especially for critically located tumours. In addition, a bloodless operative field allows easy and precise dissection and reduces the duration of surgery, which is illustrated by the fact that volume of transfusion and duration of operation are interdependent risk factors. A flawless technique is mandatory if one is to achieve total venous control. This requires adequate positioning of the caval clamps to exclude all venous collaterals, and might involve ligation of adrenal, phrenic, lumbar and accessory hepatic veins. Recognition and clamping of a possible left hepatic artery should not be neglected either[13].

Haemodynamic tolerance to TVE was excellent in most patients. Transient and moderate decreases in systemic blood pressure were observed. A slight vascular overload is essential and was always obtained before vascular occlusion to secure good haemodynamic tolerance, as it has been shown that clamping of the vena cava induces a 50 per cent decrease in cardiac index[20,21]. Venous occlusion was abandoned in only two patients because of persisting severe hypotension. Bad haemodynamic tolerance can indicate the need for associated aortic clamping, a technique used routinely in other institutions[15]. However, reported complications of spinal cord ischaemia, renal failure or aortic injury[23] make routine aortic clamping inappropriate in view of the excellent haemodynamic tolerance generally obtained without aortic occlusion.

The concept of poor tolerance of the liver to warm ischaemia has been challenged recently and it has been shown that hepatic vascular exclusion can be performed safely for up to 1 h. Duration of ischaemia up to 2 h without major detrimental effects other than transient hepatic failure has even been reported[14,22,24]. This series, in which nine patients had vascular exclusion exceeding 45 min, confirms this good tolerance, and shows that, within the limit of 60 min, there is no correlation between duration of ischaemia and morbidity. It appears that risks related to haemorrhage are of a greater concern than those related to the length of ischaemia. Thus, for critically situated and not easily resectable lesions, it is safer to continue vascular exclusion, within a 1-h limit, until complete resection is achieved, rather than take the chance of significant bleeding for the sake of a shorter period of ischaemia. Furthermore, it is possible to reduce the duration of continuous warm ischaemia, by initiating parenchymal transection without vascular exclusion or with intermittent portal triad clamping until the hepatocaval intersection is reached as used in 13 patients in this series. Intermittent portal triad clamping can be done, if needed, intermittently in successive periods of up to

20 min for more than 2 h[25]. Finally, whenever TVE is planned after analysis of radiological images, preparatory dissection of the vena cava is done, but TVE is actually carried out only if intraoperative conditions require it.

Resection of a cirrhotic liver is limited in terms of extent of resection and duration of vascular exclusion. Cirrhosis precludes major hepatectomy and prolonged vascular exclusion because of the high risk of fatal hepatocellular failure[26-28]. Therefore, whenever a major hepatectomy is planned in patients under suspicion of abnormal liver parenchyma (i.e. patients with B virus or C virus chronic hepatitis, or after chemotherapy or radiotherapy), a biopsy of the planned remnant parenchyma is done, and if cirrhotic the surgical strategy is adjusted. However, a recent paper reported no deaths in a series of selected patients with cirrhosis undergoing liver surgery under TVE[28].

The mortality rate of zero in this series confirms the safety of the technique and compares favourably with other studies[15,18,22,23,28,29]. On the other hand, a morbidity rate of 24 per cent (ten of 41 patients) cannot be dismissed as trivial, but it is none the less acceptable in view of the difficult resections involved here, as confirmed by the duration of these operations. A recent prospective randomized trial comparing intermittent clamping of the portal triad and TVE has demonstrated the lower morbidity of the former technique[30]. However, TVE in this series has been found to be safe, with no deaths, acceptable morbidity, and a remarkable limitation of blood loss and transfusion requirements.

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Prospective randomized trial of systemic antibiotics in patients undergoing liver resection

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Background Systemic antibiotics are administered frequently after hepatectomy to prevent infective complications, but their effectiveness is uncertain.

Methods A total of 127 patients with liver tumours were prospectively randomized into two groups after hepatectomy: in group 1 (62 patients) no antibiotics were given until the appearance of infective complications; in group 2 (65 patients) intravenous cephazolin 1 g every 6 h and gentamicin 80 mg every 8 h were given for 7 days. On the day before surgery all patients received bowel preparation by clear liquid diet and oral antibiotics (neomycin 1 g and erythromycin 1 g, given together in three doses).

Results The infective complication rate was 23 per cent in both groups ($P = 0{\cdot}95$). The hospital costs were higher in group 2 ($P < 0{\cdot}001$). Of the group 1 patients, 51 (82 per cent) did not require antibiotic treatment. No patient in either group died after hepatectomy.

Conclusion Postoperative systemic antibiotics cannot prevent infective complications, and their routine use after hepatectomy is unnecessary and costly. The use of antibiotics should be delayed until infective complications and persistent septic symptoms occur.

In spite of low postoperative mortality, the morbidity rate of liver resection is between 20 and 50 per cent[1-7]. Among the complications, infection is common and potentially fatal[3-7].

Antibiotic prophylaxis has been reported as unnecessary following clean surgery unless a prosthesis is used or the patient is immunocompromised[8,9]. Although liver resection is not a heavily contaminated procedure[8], it usually requires a long operating time and results in significant blood loss[1-7,10]. Many catheters are inserted for perioperative haemodynamic and urinary output monitoring, and these catheters may be the source and site of infection[8].

After liver resection, large dead spaces and areas of devitalized tissue on the cut surface are present[5,6]. If contaminated with bile or bacteria, intra-abdominal infection readily occurs[5-7]. Moreover, liver resection may reduce the functional capacity of the reticuloendothelial system[5,7] and cause translocation of intestinal bacteria to the systemic circulation[11]. Thus, the posthepatectomy infection rate may be high, and postoperative systemic antibiotics are administered routinely in most centres[1,3-7]. However, the efficacy of this strategy remains uncertain[7] in the absence of controlled data. This paper reports a randomized clinical trial of systemic antibiotics after liver resection to determine its value.

Patients and methods

Between October 1994 and September 1996, 127 consecutive patients who underwent elective liver resection for hepatic lesions were enrolled in the study. Patients who required hepatectomy for emergency conditions (such as liver trauma or ruptured liver tumour), who had associated septic circumstances (such as hepatolithiasis or hilar cholangiocarcinoma[7,12,13]) or synchronous metastatic gastrointestinal cancers[14] were excluded. Informed consent was obtained from each patient before surgery.

Preoperative assessments included liver function testing, indocyanine green (ICG) clearance testing and imaging studies (including abdominal ultrasonography, computed tomography (CT) and angiography)[15]. Child's grading for liver cirrhosis[16] was applied to each patient. On the day before surgery all patients received a clear liquid diet and oral antibiotics (neomycin 1 g and erythromycin 1 g, given together at 13.00 hours, 14.00 hours and 22.00 hours) for bowel preparation as suggested by Condon and Wittmann[9].

Couinaud's definition of liver segmentation[17] was used for reporting the tumour location and the extent of hepatectomy. The amount of liver resection was determined by the preoperative liver function and ICG clearance testing[1,2,15].

All operations were performed under general anaesthesia with endotracheal intubation, and central venous, arterial and urethral catheters were inserted. Cholecystectomy was performed routinely before hepatectomy. Liver parenchymal dissection was carried out by the Kelly fracture method, usually under intermittent occlusion of hepatic inflow blood[1,2,15]. After removal of all lesions, the cut surface of the liver was packed with Surgicel (oxidized cellulose; Johnson and Johnson Medical, Arlington, Texas, USA) and surrounded with closed suction drains[5]. The drains were retained until the drainage fluid appeared serous and the amount was less than 50 ml per day.

Immediately after operation, all patients were randomized into two groups without regard to patient background or operative procedure. Group 1 comprised 62 patients to whom no antibiotics were given after the operation. Group 2 consisted of 65 patients who received intravenous cephazolin 1 g every 6 h and gentamicin 80 mg every 8 h for 7 days beginning immediately after operation. These antibiotics were chosen because of possible contamination with bile during hepatectomy[3,5-7], as well as their high biliary secretion[18] and high efficacy in biliary surgery[19].

As with previous reports[3-9,18,20-22], infective complications were defined as positive culture of pathogenic micro-organisms from infective sites, such as wound, tip of central venous catheter,

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urinary or respiratory tract, and abdominal cavity. Sensitivities to various antimicrobial agents were determined when bacteria were cultured.

If postoperative septic symptoms (fever, chills, undue wound pain or leukocytosis) occurred, the potential infective sites were examined, and management of infective complications was instituted immediately after diagnosis. Management and treatment involved opening the infected wound, removing the infected catheter or draining the intra-abdominal abscess. Cephazolin and gentamicin were prescribed or continued (for group 2 patients whose infections occurred within 7 days after operation) or changed to more appropriate antibiotics based on the bacteriological sensitivities.

Operative morbidity and mortality were defined as complications and deaths occurring within 30 days after the operation or during the same hospitalization. The clinicopathological characteristics, surgical procedures and operative results of the patients were compared between the two groups. Continuous variables were expressed as mean(s.d.) and were compared using Student's *t* test. Frequencies were compared with the χ^2 test. $P<0·05$ was considered significant.

Results

Background characteristics of the patients

The indications for liver resection and background patient characteristics are shown in *Table 1*. There were no significant differences in tumour pathology or any demographic category between the two groups.

Surgical procedures and intraoperative results

There were no significant differences in any category between the two groups (*Table 2*). Only one patient in group 1 and four in group 2 did not require the hepatic

Table 1 Surgical indications and demographic characteristics of patients who underwent liver resection

	Group 1 (*n* = 62)	Group 2 (*n* = 65)	*P*
Indication			0·55*†
Primary malignancy			
Hepatocellular carcinoma	50	52	
Intrahepatic cholangiocarcinoma	0	1	
Leiomyosarcoma	0	1	
Total	50*	54*	
Secondary malignancy			
Metastatic colonic cancer	6	3	
Metastatic gastric cancer	0	1	
Gallbladder carcinoma	0	1	
Metastatic breast cancer	1	1	
Metastatic carcinoid	1	0	
Metastatic nasopharyngeal cancer	1	0	
Total	9*	6*	
Benign lesion			
Haemangioma	2	3	
Cystadenoma	1	1	
Biliary harmatoma	0	1	
Total	3*	5*	
Mean(s.d.) age (years)	58·5(12·2)	56·9(12·4)	0·45‡
Sex ratio (M:F)	44:18	43:22	0·56†
Associated systemic disease			
Diabetes mellitus	2	3	
Hypertension	4	7	
Coronary heart disease	1	2	
Old cerebral infarction	1	3	
Chronic obstructive lung disease	3	1	
Pulmonary tuberculosis	1	0	
Gouty arthritis	0	1	
Thalassaemia	1	2	
Total	11	16	0·34†
Associated cirrhosis	48	56	0·20†
Previous history of laparotomy	21	16	0·25†
Previous history of hepatectomy	9	6	0·36†
Serum HBsAg positive	31	27	0·34†
Child grade			
A	52	57	0·82†
B	9	7	
C	1	1	
Mean(s.d.) ICG R15 (%)	13·9(5·8)	13·1(5·4)	0·42‡
Mean(s.d.) tumour size (cm)	5·8(3·7)	6·3(4·5)	0·47‡
Tumour number			
Solitary	47	53	0·43†
Multiple (≥2)	15	12	

*Comparison of surgical indications between the two groups. HBsAg, hepatitis B surface antigen; ICG R15, indocyanine green 15-min retention rate. †χ^2 test; ‡Student's *t* test

Table 2 Surgical procedures and intraoperative results

	Group 1 ($n = 62$)	Group 2 ($n = 65$)	P
Extent of liver resection			0·32†
≥3 segments*	15	19	
2 segments*	15	21	
≤1 segment*	32	25	
Concomitant resection of other organs			0·55†
Diaphragm	5	6	
Spleen	3	1	
Stomach	1	1	
Adrenal gland	1	0	
Colon	1	1	
Duodenum	1	0	
Common bile duct	0	1	
Total	12	10	
Mean(s.d.) operating time (h)	5·54(2·44)	5·76(1·80)	0·42‡
Mean(s.d.) operative blood loss (ml)	1203(965)	1218(785)	0·93‡
Mean(s.d.) blood transfusion (ml)	316(549)	392(620)	0·47‡
Mean(s.d.) resected liver weight (g)	237(298)	290(432)	0·43‡

*Liver segments were defined according to Couinaud[17]. †χ^2 test; ‡Student's t test

inflow blood occlusion technique. Mean(s.d.) total liver ischaemic time did not differ significantly between the two groups (44·8(26·4) min in group 1 *versus* 41·2(26·5) min in group 2; $t = 0·75$, 120 d.f., $P = 0·46$).

Postoperative course

Postoperative complications occurred in 16 patients in each group ($\chi^2 = 0·02$, 1 d.f., $P = 0·88$). Infective complications occurred in 14 (23 per cent) group 1 patients (consisting of two central venous catheter infections, three urinary infections, two wound infections, three pulmonary infections, five intra-abdominal absesses and one case of parotitis) and 15 (23 per cent) group 2 patients (one central venous catheter infection, five urinary infections, one wound infection, one pulmonary infection and eight intra-abdominal abscesses). Bile leakage developed in three group 1 and five group 2 patients, and caused intra-abdominal abscess in four patients (two in each group). Of the patients with intra-abdominal abscess, ten (four in group 1 and six in group 2) required percutaneous catheter drainage[6,10]. The remaining patients were treated by intraoperative placement of drainage tubes. All patients with bile leakage recovered completely within 1·5 months of operation. Wound dehiscence developed in one patient in group 2 following infection and required repair.

Non-infective complications occurred in five group 1 patients (consisting of one patient with prolonged jaundice, two with ascites and two with pleural effusions) and three group 2 patients (two with ascites and one with a pleural effusion). One patient had bile leakage and prolonged jaundice for 3 weeks and healed spontaneously. There were no significant differences between the groups with respect to the infective ($P = 0·95$) and non-infective ($P = 0·49$) complication rates. No patient in either group died after hepatectomy.

Bacteriology and antibiotic usage

Staphylococcus aureus was the most frequently cultured micro-organism (seven in group 1, five in group 2), with five (one in group 1, four in group 2) being methicillin resistant. The other bacterial isolates included *Candida* in eight patients (three in group 1, five in group 2), *Klebsiella* in four (three in group 1, one in group 2), *Streptococcus* in five (three in group 1, two in group 2), *Escherichia coli* in three (one in group 1, two in group 2), *Pseudomonas* in three (one in group 1, two in group 2), *Proteus* in three (two in group 1, one in group 2), *Veillonella* in one (group 1), *Acinetobacter* in one (group 1) and *Staphylococcus epidermidis* in one (group 2). Bacteraemia developed in two patients with intra-abdominal abscess (*Klebsiella* in group 1 and *Candida* in group 2).

Of the 14 group 1 patients with infective complications, 11 required antibiotic therapy. Two patients with urinary infection and one patient with a central venous catheter infection did not need antibiotics as the septic symptoms were immediately relieved by removal of the infected catheter. A total of 51 group 1 patients (82 per cent) did not receive any systemic antibiotics during the entire course. Of the group 2 patients with infective complications, a change of antibiotics was required in 11 patients as the prescribed antibiotics were ineffective.

There were no side-effects from the antibiotics used in this study. Although the mean(s.d.) postoperative hospital stay did not differ significantly between the two groups (13·0(7·5) days for group 1 *versus* 14·5(7·8) days for group 2; $t = -1·17$, 125 d.f., $P = 0·24$), the mean(s.d.) total hospital costs in group 2 were significantly higher (US\$7494(3564) *versus* US\$9185(5363); $t = -3·72$, 112 d.f., $P < 0·001$).

Discussion

As liver resection has been associated with a high rate of susceptibility to infection, many authors have proposed potential factors that may lead to an increase in infection rate in such patients[3–7,11,14,22]. These factors include the presence of diabetes mellitus, cirrhosis, chronic pulmonary disease, surgical extension to the thorax, previous liver surgery, wide extent of resection, long operating time and a large volume of operative blood loss[3–7,11,14]. However, there were no significant differences between the present two groups with respect to the above factors. Therefore, using the same postoperative management, the operative results of both groups were comparable.

Antibiotic prophylaxis for infective complications after elective non-contaminated surgery is generally not necessary[8,9]. However, recent controlled studies suggest that prophylactic antibiotics may provide benefits to some high-risk patients undergoing simple and clean procedures[20,21] or elective biliary surgery[18].

In this study, to avoid any bias of surgical decision-making during the operation, randomization was performed following operation and systemic antibiotics were not used before surgery. Theoretically, such antibiotics had no prophylactic effect on infective complications. However, the authors used a recommended preoperative protocol of bowel preparation and oral antibiotics[9], as a considerable serum level of erythromycin during operation may play some role in reducing the perioperative infection rate[9]. This study was performed to evaluate the effectiveness of systemic antibiotics for the prevention of posthepatectomy infection.

Infective complications occurred at similar rates in both groups. Some of the infective complications were related to operative technique (such as wound infection or intra-abdominal abscess). As good antibiotics cannot cover a bad surgery[8,9], postoperative systemic antibiotics cannot prevent such infections. Although the antibiotics in this study were selected for their high biliary secretion, septic symptoms still developed in patients with biliary leakage, and some patients required a change of antibiotics. Moreover, postoperative antibiotics were also unable to prevent technique-unrelated infections (such as respiratory or urinary tract infection, central venous catheter sepsis or parotitis).

In this study, no patient showed adverse side-effects from the selected antibiotics. However, the incidence of so-called 'opportunistic nosocomial infections'[8,9,22], such as fungal and methicillin-resistant *S. aureus* infections, was higher in group 2 patients, although the difference was not statistically significant. Such micro-organisms are resistant to generally used antibiotics and thus other more expensive antibiotics may be required[8,9,22]. In this study, the hospital costs were higher in group 2 patients than in group 1 patients, even though the length of hospital stay was similar in both groups.

As a result of the widely accepted use of antibiotic prophylaxis after liver resection[3–7,9,22], the possibility of performing hepatectomy without systemic antibiotic coverage has never been reported. With a reduction in operative bleeding, preservation of functioning liver[15], careful postoperative observation and early treatment of infective complications, it was found that some minor infections could be cured without antibiotics. Thus, more than 80 per cent of group 1 patients, even those with high-risk factors, could tolerate hepatectomy without needing systemic antibiotics.

Bacteraemia occurred in two patients with intra-abdominal abscess in this series. This condition can be fatal if not treated in time[5–7]. Because diagnosis of intra-abdominal abscess after hepatectomy is difficult[6], when septic symptoms occur after hepatectomy, and other possible sites of infection are not discovered, prompt imaging studies such as abdominal ultrasonography or CT should be performed, rather than prescribing antibiotics[6,7,10]. Moreover, avoidance of posthepatectomy infections, by early removal of the monitoring catheters, fine dissection of liver parenchyma, reduction of devitalized tissue in dead spaces, and careful haemostasis and closing of the transected tiny bile ducts during hepatectomy, is more important than the use of antibiotics.

It is concluded that most patients tolerate liver resection without systemic antibiotics. Routine use of antibiotics after elective liver resection is both unnecessary and costly. Antibiotics cannot prevent postoperative infections, and their use can be delayed until infective complications occur.

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Encouraging results of split-liver transplantation

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Background Liver donor shortage presently accounts for a 10 per cent waiting list mortality rate. Split-liver transplantation (SLT) can improve utilization of this scarce resource.

Methods Twenty-four SLTs (11 left, 13 right grafts) from 13 livers were performed in 23 patients (nine adults, 14 children), comprising 4·5 per cent of all orthotopic liver transplants (14 urgent or emergency, ten elective). The left graft comprised segments II and III, whereas the right graft comprised segments V–VIII in eight cases, IV–VIII in three, and segments I, IV–VIII, and I, V–VIII in one case each. Additional arterial extension grafts were required in six of 24 cases, and portal venous interposition graft in one.

Results Twenty-one grafts showed good initial function, with one primary non-function and two initial poor function. The median peak aspartate aminotransferase level was 782 (range 94–2301) and 982 (range 382–2520) units/l for left and right grafts respectively. Five patients died (all urgent recipients), all within the first 30 days after surgery. Two SLT recipients underwent subsequent retransplantation. All ten elective recipients are alive. The 1-year actuarial patient and graft survival rates at a median follow-up of 20 months were 78 and 68 per cent respectively.

Conclusion These encouraging results compare favourably with those of reduced-size and whole-liver transplantation and justify wider application of this technique, thereby optimizing donor resource use.

The shortage of livers from cadaveric donors is the main factor preventing growth in liver transplantation programmes. The introduction of reduced-size liver transplantation (RLT), where only part of a liver is transplanted, has improved the availability for paediatric recipients[1-3]. Living related liver transplantation (LRT) has also had a favourable impact on paediatric transplantation in several countries[4-6]. However, LRT is not applicable to most adult recipients. These innovative techniques have reduced waiting time and mortality in children, particularly in those less than 1 year old or weighing less than 10 kg[1,2]. The success of orthotopic liver transplantation (OLT), with most centres reporting survival rates of over 80 per cent after transplantation, has resulted in a relaxation of the selection criteria, leading to larger waiting lists with more debilitated potential recipients. Consequently, waiting list mortality has increased and approximately 10 per cent of patients die before a suitable organ becomes available[6-8].

In split-liver transplantation (SLT), two grafts are obtained from a single cadaveric donor liver. The left lateral segment (segments II and III) is transplanted into a paediatric recipient and the right hemiliver into an adult or larger paediatric recipient[9-12]. This results in increased paediatric organ availability without compromising the adult donor pool[3,8,13]. The early experience of SLT involved its application in extreme clinical situations with an outcome inferior to established techniques of whole OLT and RLT[3,8-12]. This paper evaluates SLT in Birmingham, UK: the logistical problems associated with SLT, surgical techniques, complications, and patient and graft outcome.

Patients and methods

Between November 1992 and April 1996, 486 patients (390 adults, 96 children) underwent 535 OLTs (427 adults, 108 children). These included 24 SLTs (4·5 per cent of OLTs) from 13 donor livers carried out in 23 patients. Two livers were split at another liver unit where the left grafts were retained. The recipient demographic details were as follows: nine adults (six women, ten grafts, median age 49 (range 25–60) years); 14 children (nine girls, median age 2 years (range 9 months to 11 years)). Fourteen of 24 grafts were carried out as urgent ($n = 11$, hospital-bound patients or in intensive care) or super-urgent ($n = 3$, acute liver failure) transplants, equivalent to United Network for Organ Sharing (UNOS) status 1 or 2, with ten carried out in elective (UNOS 3 or 4) recipients (*Table 1*). All transplants were carried out as sequential procedures with a median cold ischaemia time (CIT) of 603 (range 435–921) min for the first graft and 102 (range 870–1326) min for the second. Immunosuppression was based on triple drug therapy with cyclosporin, azathioprine and steroids with an aim to stop steroids at 3 months[14,15].

Donor details

Median donor age was 21 (range 7–42) years; blood group, O ($n = 9$), B ($n = 3$) and A ($n = 1$); median weight 67 (range 22–100) kg. The cause of death was trauma in six, intracranial bleed in four and 'other' in three (hypoxia following status asthmaticus, hydrocephalus, cerebral infarction). All donors were ABO identical and preserved with University of Wisconsin solution. Iliac vessels were retrieved to be used as extension grafts if necessary. Arterial anatomy was anomalous in three of 13 cases: right hepatic from superior mesenteric artery ($n = 2$) and left hepatic from left gastric artery ($n = 1$).

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Table 1 Indications for split-liver transplantation in adults and children

Adults	
Primary grafts	
Primary biliary cirrhosis	3
Non-A, non-B hepatitis	2
Primary sclerosing cholangitis	1
Wilson's disease	1
Hepatitis C	1
Alcohol	1
Regrafts	
Hepatic artery thrombosis	1
Children	
Primary grafts	
Biliary atresia	5
Biliary hypoplasia	1
Hepatoblastoma	1
Chronic active hepatitis	1
Propionic acidaemia	1
Methylmalonyl acidaemia	1
Hepatitis A	1
Regrafts	
Chronic rejection	2
Hepatic artery thrombosis	1

Bench splitting procedure, vascular and biliary reconstruction

Cholangiography to delineate segmental biliary anatomy was carried out before splitting and showed conventional bifurcation of left and right ducts in 11 livers, an immediate bifurcation of the right duct into segment VI, VII and segment V, VIII ducts amounting to a 'trifurcation', and drainage of the segment VI, VII duct into the left duct as the other anomaly. Arteriography was not performed as arterial variations were identified during the hilar dissection. The main hepatic arterial trunk was retained with the left graft in eight livers and the right graft in five. Arterial interposition grafts were required in six SLTs: three left and three right grafts. In the remaining 18 patients no extension grafts were used as the recipient artery was anastomosed directly to the donor vessel as follows. (1) Left graft: donor hepatic trunk in five, donor left hepatic artery in three; and (2) right graft: donor hepatic trunk in five, donor right hepatic artery in three and the replaced right hepatic from superior mesenteric artery in two. The three donor hepatic arterial anomalies facilitated splitting and both grafts were prepared with an adequate donor artery. All arterial anastomoses were carried out using magnification loupes. The main portal trunk was retained with the left graft in 11 livers and the right graft in two. Only one donor iliac vein interposition graft was used (the first SLT) from the recipient portal vein to the donor left portal vein. In 23 of 24 SLTs the recipient vein was anastomosed directly to the donor right portal vein ($n = 11$), main vein ($n = 11$; nine left, two right grafts) or left vein ($n = 1$).

A blunt lachrymal probe was then passed up to the biliary bifurcation and the left duct divided, always retaining the common duct with the right graft. Biliary reconstruction was as follows: left duct to jejunal Roux loop for all 11 left grafts; duct-to-duct anastomosis in eight (one with a T tube), and a main duct to jejunal Roux loop in five of the 13 right grafts. The donor main duct was shortened until satisfactory bleeding was observed before commencing the biliary anastomosis, carried out with 5/0 polydioxanone (PDS; Ethicon, Edinburgh, UK). The left hepatic vein was divided at its junction with the inferior vena cava (IVC), the IVC oversewn and retained with the right graft. The parenchymal hepatic division was carried out by haemostat dissection and bipolar diathermy, carefully ligating all biliary and vascular branches. The cut surface was then sprayed with fibrin glue (Tisseal; Immuno, Vienna, Austria). There were 11 left grafts (segments II and III) transplanted into nine children and two adults; and 13 right grafts comprising segments V–VIII in eight; IV–VIII in three; I, IV–VIII and I, V–VIII in one patient each, transplanted into eight adults and five children. More recently the split procedure has been simplified to retain segments I and/or IV whenever possible, thereby limiting the parenchymal division phase.

The following factors were studied: early graft function, perioperative complications, patient morbidity, mortality, and graft and patient survival. Statistical analyses were carried out using Fisher's exact test, and survival was calculated with the Kaplan–Meier method.

Results

Perioperative complications, graft function and outcome

Of 24 SLTs, 21 showed good initial function. There was one primary graft non-function (PNF) (defined as non-life-sustaining graft function resulting in death or retransplantation within the first week), and two with initial dysfunction (poor early graft function with prolonged intensive care stay, peak aspartate aminotransferase (ASAT) level more than 2000 units/l, prothrombin time of over 16 s for days 2–7 after OLT). Median peak day 1–5 ASAT concentration was 782 (range 94–2301) and 982 (range 382–2520) units/l for left and right grafts respectively. There were five deaths, all in urgent or super-urgent recipients (three children, two adults; three right grafts, two left grafts; one first recipient with shorter CIT, four second recipients with longer CIT; P not significant), within the first 30 days. Causes of death were: PNF, non-thrombotic graft infarction, metabolic crisis in a child transplanted for methylmalonyl acidaemia, intracranial bleed and respiratory sepsis. The first two patients died before a suitable replacement graft could be found. Two patients having SLT underwent retransplantation for hepatic artery thrombosis (HAT) (at 3 weeks) and chronic rejection (at 7 months). Other complications recorded were relaparotomy for bleeding ($n = 1$), perihepatic haematoma ($n = 1$), pulmonary sepsis ($n = 2$), technical splenectomy ($n = 1$), anastomotic biliary stricture ($n = 2$, treated by biliary reconstruction) and a bile leak from the cut surface with an anastomotic stricture treated by pigtail catheter drainage, anastomotic dilatation and internal–external biliary drainage in one patient.

The left lateral segment was transplanted into an adult recipient twice (both small women, recipient weights 43 and 60 kg, donor weights 85 and 100 kg respectively). The first showed satisfactory initial function, but developed acute rejection and hepatic insufficiency during the second week after SLT and died from multiple organ failure secondary to non-thrombotic graft infarction before a replacement graft could be found. The second patient received this as an emergency regraft for HAT 16 days after a right SLT, with the left lateral segment weighing 760 g. All ten elective recipients are alive, one having undergone a second SLT for HAT. Median follow-up was 20 (range 8–48) months. The overall 1-year actuarial patient and graft survival rates were 78 and 68 per cent respectively.

Discussion

The innovative techniques of RLT and LRT have significantly improved organ availability in children with a reduction in mortality on waiting lists from about 15 to 5 per cent[1–3,8]. RLT, however, results in diversion of organs from the adult to the paediatric recipient pool. Donor criteria have been relaxed and many centres accept a significant proportion of marginal-quality donor livers[17,18]. One way of increasing the donor pool would be to make wider use of SLT, without diversion of organs from the adult to the paediatric pool. The early experience involved application of a new procedure in high-risk patients, often as a desperate measure, and this was reflected in a high morbidity rate[9–12]. SLT results have improved with experience and standardization of techniques[8,13,19,20], and the overall 1-year patient and graft survival rates (78 and 68 per cent respectively) for this series with a high proportion of high-risk patients compares favourably with RLT and whole OLT, and are superior (100 per cent (ten of ten patients) survival rate) in elective low-risk patients. The Paris[19] and Hamburg[20] groups have also recently shown improved results in elective recipients, underlying the importance of recipient selection. Donor selection is crucial and marginal donors, as previously defined, were not considered for SLT[17]. As regards technical details, in most instances the main portal venous and arterial trunks are allocated to the left graft, and the IVC and main bile duct always to the right graft. By dividing recipient vessels high in the hilum, the use of vascular extension grafts is minimized and only seven such extension grafts were needed (one venous, six arterial). Rat *et al.*[21] suggest allocation of the main portal vein to the right graft on the basis of an anatomical study of livers taken at post-mortem examination. However, as the left graft is implanted into a paediatric recipient, where the recipient portal vein often needs to be dissected back, the extra length of the main donor vein is essential to provide adequate length. For the right graft the donor right portal vein is anastomosed to the recipient vein.

There was only one case of HAT and the patient underwent retransplantation. This compares favourably with the incidence of vascular thrombosis following RLT and whole OLT[22–24]. Biliary complications were seen in three of the 24 patients. Necrosis of the main bile duct was not seen in cases where the main hepatic arterial trunk was retained with the left graft. All left grafts had a single-lumen left duct anastomosed to a jejunal Roux loop. The incidence of double left ducts is higher with *in situ* SLT where the left duct is divided at a level just to the right of the falciform ligament[20,25,26]. Bench cholangiography was helpful in delineating segmental bile duct anatomy; it identified two anatomical variations, and is an important step before proceeding with splitting. The bench split can be simplified by retaining segments I and IV with the right graft. Both these segments derive their arterial and portal venous perfusion from both the right and left branches. Segment I perfused well in both cases where it was retained, although a strip of hypoperfusion along the cut edge of segment IV was seen in two of four cases where segment IV was retained. This did not influence graft outcome.

There are several logistical aspects that need to be taken into consideration before SLT is set up. Close coordination between the donor, splitting and recipient teams is essential, to minimize CIT. In the authors' unit it is not yet possible to carry out two grafts simultaneously, and all SLTs were carried out sequentially; this did result in longer CIT for the second grafts. A majority of the recipients were either high risk or super-urgent (UNOS 1 or 2), and most of the early experience involved transplanting two high-risk recipients. The present approach is to select one high-risk and one elective recipient, if possible, to minimize pressure on theatre and intensive treatment unit resources.

Four of the five patients (*P* not significant) who died received the second graft of the split, although only one of these deaths was a result of poor graft function. Several approaches have been adopted to minimize CITs. Others are increasingly adopting *in situ* splitting at the donor hospital, where the left lateral segment is resected before the aorta is clamped and donor perfusion commenced, in an attempt to decrease CIT and promote organ sharing[20,24,25]. Most donor hospital theatres are not equipped for such a procedure, which adds up to 2 h to the length of the retrieval operation, and does delay cardiac and renal teams. This is one advantage of the *ex situ* split compared with *in situ* splitting. The sharing of SLTs between units reduces CITs, and this is being practised increasingly by many European centres[19,20]. Earlier SLT experience suggested that the right graft is potentially compromised compared with a whole graft, with a higher chance of surgical complications. Both left and right grafts in this series were of equal quality, with no difference in outcome. In two instances the left lateral segment was transplanted into an adult recipient. One concern in this situation is that, if there is some degree of initial dysfunction and/or the patient experiences an acute rejection episode, hepatic insufficiency may develop.

In conclusion, the results of SLT compare favourably with those of reduced- and whole-liver transplantation. Standardization of surgical techniques, careful selection of donors and recipients, and measures to reduce CIT such as increased sharing will permit its wider application, resulting in better use of the limited donor liver pool.

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Carcinoma of the head of the pancreas arising from the uncinate process

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Background Carcinoma located in the uncinate process (CUP) of the pancreatic head is considered to be rare. Exact epidemiological data, however, are not available because the series published so far consist of fewer than ten patients. The purpose of this prospective study was to evaluate the clinical appearance of CUP and to compare findings with those of patients with carcinoma in the ventral aspect of the pancreatic head (VPC), which represents the most frequent localization.

Results Some 39 (8 per cent) of 506 evaluated patients suffered from CUP. Mean age was 63·3 years. The most frequent complaints were upper abdominal pain ($n = 32$) and weight loss ($n = 35$). Jaundice was seen in only five patients and was never an early symptom. The level of CA19-9 was raised in 33 patients. The best diagnostic procedure to detect CUP was computed tomography (CT) (sensitivity 93 per cent), whereas endoscopic retrograde cholangiopancreatography was not useful (sensitivity 21 per cent). Vascular involvement was significantly ($P < 0·01$) more common in CUP ($n = 19$) than in VPC (48 *versus* 19 per cent). This finding and the fact that most patients with CUP were diagnosed at a late stage with distant metastasis or severe vascular involvement present ($n = 21$) are responsible for the significantly lower rate of operation ($n = 25$) (64 *versus* 92 per cent, $P < 0·05$) and the significantly shorter median survival time (5 *versus* 11 months, $P < 0·05$).

Conclusion Patients with CUP have a poor prognosis as a result of the lack of early symptoms (jaundice) and early vascular involvement due to the proximity of the uncinate process to the mesenteric root. A raised level of CA19-9, together with weight loss and/or upper abdominal pain, should prompt CT.

The uncinate process arises from the embryological dorsal aspect of the pancreas. Anatomically it represents a hook-like extension of the lower part of the pancreatic head It is located just posterior to the superior mesenteric vessels along the upper border of the third portion of the duodenum. Its different embryological origin, apart from the larger ventral aspect of the pancreas, is reflected in the absence of endocrine activity due to lack of islets of Langerhans, thus resulting in a different histological appearance. The development of a malignancy within this pancreatic region is considered to be rare, but exact epidemiological data are not available.

Few authors have reported the clinicopathological findings associated with a pancreatic neoplasm arising in this area. These reports have been based on a limited number of patients: Suzuki *et al.*[1] reported on six patients and Yamaguchi[2] described three. The purpose of this study was therefore: (1) to evaluate the clinical appearance of carcinoma within the uncinate process (CUP) in a larger series of patients and to compare the findings with those in patients suffering from carcinoma within the ventral aspect of the pancreatic head (VPC); and (2) to assess the impact of modern imaging procedures and surgical techniques on outcome in these patients.

Patients and methods

This prospective study included data on 506 patients admitted to this department between 1982 and 1994 because of pancreatic malignancy. The patient's history, symptoms, validity of all diagnostic measures, therapy and outcome were recorded and entered into a database. The study included only patients who had a complete diagnostic assessment, which consisted of transcutaneous ultrasonography, contrast-enhanced computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP), and angiography of the coeliac trunk, superior mesenteric artery and venous portal system.

CUP was defined as a pancreatic tumour localized within the uncinate process (i.e. dorsal aspect) as determined by intraoperative and/or localization data provided by the applied imaging systems.

To detect significant differences in symptomatology, and in the value of diagnostic measures as well as therapy and outcome, these parameters were compared between the two groups of patients (CUP *versus* VPC) applying χ^2 and Student's t tests. $P < 0·05$ was considered statistically significant.

Results

Some 39 (8 per cent) of 506 patients (21 men) suffered from carcinoma of the pancreatic head located in the uncinate process. Mean age was 63·3 (range 48–79) years.

Symptoms

The main complaint was upper abdominal pain especially after meals in 32 patients and weight loss exceeding 10 per cent of original body-weight in 34 (*Table 1*). The median interval between the onset of these first symptoms and confirmation of the disease was significantly longer in patients suffering from CUP than in those with VPC. Most patients ($n = 24$) had consulted a physician within this period. Frequently the primary diagnosis was thought

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Table 1 Main symptoms of patients with carcinoma of the uncinate process or of the ventral pancreatic head

Symptom	CUP ($n=39$)	VPC ($n=465$)	P
Weight loss	34	316 (68)	n.s.
Abdominal pain	32	320 (69)	n.s.
Jaundice	5	334 (72)	<0·001*
Diarrhoea	24	288 (62)	n.s.
Nausea	20	195 (42)	n.s.
Interval between onset of symptoms and diagnosis (weeks)	22	10	<0·05†

Values in parentheses are percentages. CUP, carcinoma of the uncinate process; VPC, carcinoma of the ventral pancreatic head; n.s., not significant. *χ^2 test, †Student's t test

to be various forms of gastroduodenitis and/or gastroduodenal ulcer ($n=21$) and the patients were treated accordingly. The correct diagnosis was not established until second-line imaging procedures, such as CT or ERCP, were employed.

Jaundice was seen in only five patients with CUP and was never observed as an early symptom.

Laboratory findings

On admission to hospital no specific alterations in laboratory parameters were observed except for anaemia in 12 of the 39 patients and raised liver enzyme levels in eight. The tumour marker CA19-9 was raised in 33 of the 39 patients with CUP, with a mean value of 462 (range from 14 to more than 4000) units/ml (normal value 37 units/ml or less). Due to the lack of jaundice in patients with CUP, false-positive values due to raised serum bilirubin levels were not found in this series (specificity 96 per cent).

Imaging techniques

CT revealed a mass in the uncinate process in 36 of the 39 patients (*Table 2*). Three patients presented pathological CT findings, leading to the suspicion of a pancreatic anomaly within the pancreatic head; the diagnosis of CUP, however, was confirmed during laparotomy.

Transcutaneous ultrasonography was able to detect enlargement of the uncinate process in 26 patients. In VPC the sensitivity of this method was significantly higher (67 *versus* 89 per cent, $P<0\cdot01$).

Pathological findings on ERCP were obstruction or stenosis of the main pancreatic duct in five patients; three patients had stenosis of the common bile duct and one had infiltration of the duodenal mucosa. The sensitivity of ERCP in patients with VPC was significantly higher, being the only single technique reaching a sensitivity and specificity of over 90 per cent (21 *versus* 92 per cent in VPC, $P<0\cdot001$).

Table 2 Sensitivity and specificity of diagnostic procedures in carcinoma of the uncinate process

Diagnostic procedure	Sensitivity (%)	Specificity (%)	P*
Transcutaneous ultrasonography	62	78	<0·05
ERCP	21	92	<0·001
Computed tomography	93	88	n.s.
Estimation of CA19-9 level	84	96	n.s.

ERCP, endoscopic retrograde cholangiopancreatography; n.s., not significant. *Carcinoma of the uncinate process *versus* carcinoma of the ventral pancreatic head (χ^2 test)

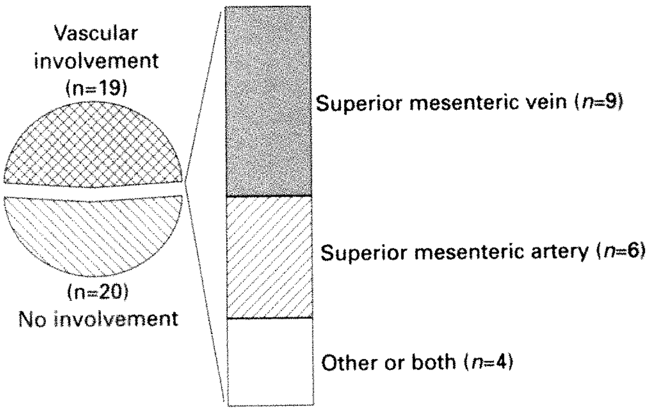

Fig. 1 Vascular involvement: incidence and localization

Angiography revealed encasement or occlusion of a major vessel in 19 patients with CUP (*Fig. 1, Table 3*), significantly more often than in VPC (19 of 39 *versus* 88 of 465, $P<0\cdot001$).

Therapy

Only 24 patients were considered primarily as candidates for operation. Ten patients presented with liver metastases at the time of diagnosis. In the absence of jaundice and/or duodenal obstruction, no immediate surgical palliation was necessary and these patients received systemic chemotherapy ($n=4$; 5-fluorouracil 2250 mg per m^2 per week), or no therapy at all if the general condition did not allow such treatment or the patient did not consent.

Angiography showed occlusion of the superior mesenteric vein and/or artery in four patients. These patients were therefore considered to suffer from an irresectable tumour and received either systemic chemotherapy in the above-mentioned protocol ($n=2$) or, after its introduction in 1992, regional chemotherapy via a coeliac trunk catheter[4].

In 12 patients resection of the tumour was performed (eight pylorus-preserving partial pancreaticoduodenectomies, four standard partial pancreaticoduodenectomies). In four of these cases the surgeon considered the operation as palliative, i.e. an R_2 resection (macroscopically residual tumour remaining according to the tumour node metastasis classification). In two patients

Table 3 Venous vascular involvement (Ishikawa classification[3]) in carcinoma of the uncinate process

Stage	Description	No. of patients ($n=30$)
I	Normal	15
II	Smooth shift	2
III	Unilateral narrowing	2
IV	Bilateral narrowing	4
V	Bilateral narrowing with collateral vein	7

involved venous segments were resected and an end-to-end anastomosis was performed; in one patient an allograft replaced the resected portal vein. Six patients underwent a bypass operation: three Billroth II resections, two choledochojejunostomies, one double bypass (Billroth II with choledochojejunostomy). Seven patients underwent exploratory laparotomy without resection or bypass, due to local irresectability ($n = 5$) or the presence of distant metastases ($n = 2$).

Major complications were seen in two patients (one anastomotic leak, one postoperative bleed); neither required reoperation. Conservatively treated minor complications were prolonged gastric emptying ($n = 2$), superficial wound infection ($n = 1$) and haematuria following intraoperative placement of a percutaneous urinary catheter ($n = 2$).

Lymph node involvement

In 12 patients in whom resection of the tumour was achieved, a complete pathological investigation was performed. In ten cases a grade II tumour was seen, in one case a grade II-III tumour and in one a grade III tumour. None of these patients was free from lymph node metastasis. The most frequent location of involved nodes was adjacent to the superior mesenteric artery and vein ($n = 7$) and the small bowel mesentery ($n = 5$).

Outcome

The median survival time after the diagnosis of CUP was 5 (range 0–11) months. This is significantly shorter than for patients with VPC (11 months) ($P < 0{\cdot}05$). The bypass group had a median survival of 5 months. When no surgical option was available ($n = 21$), median survival was 4 months (*Table 4*).

Discussion

Pancreatic carcinoma within the uncinate process is rare. In smaller previously published series Yamaguchi[2] reported an incidence of 2·5 per cent (three of 119 patients), and Suzuki *et al.*[1] found an incidence of 11 per cent (six of 56). In the present series, 39 (8 per cent) of 506 patients suffered from CUP.

The description of a rare anatomical localization for pancreatic cancer alone might be of statistical interest only. However, the authors believe that a more accurate classification than that simply of cancer of the pancreatic head, body or tail is necessary to allow proper assessment of the disease, especially if neoplasm at a rare site is accompanied by an unusual clinical appearance requiring an alternative strategy in diagnosis and therapy.

Patients with CUP in this study exhibited a few non-specific symptoms, weight loss and inconstant upper abdominal pain being the leading ones. Therefore, these patients were usually misdiagnosed on their first medical examination, a phenomenon recognized in patients with pancreatic cancer[5]. Concomitantly the time between first medical consultation and establishment of the correct diagnoses took significantly longer in patients with CUP. This seems to be due not only to the lack of specific early symptoms, especially jaundice as the cardinal symptom in the 'classical' location, but also to additional difficulties in the application of imaging techniques.

Transcutaneous ultrasonography, as the first-line imaging technique for the diagnosis of abdominal disorders, has an overall sensitivity of 70–80 per cent in pancreatic cancer[6]. Imaging of the uncinate process, however, may be hindered by overlying bowel. The embryologically dorsal aspect of the pancreas representing the uncinate process also frequently exhibits hypo-echogenicity due to different fat content[7], a fact that impairs the localization of a tumour in this area.

In the authors' experience the easily available tumour marker CA19-9 is a valuable diagnostic method with a sensitivity and specificity of more than 80 per cent[8]. Eighty-four per cent of patients investigated exhibited pathological levels greater than 37 units/ml with a specificity of 96 per cent.

CT proved to be the best diagnostic tool with a sensitivity of 93 per cent. Smaller masses in the uncinate process were detected by CT, when other techniques showed normal morphology. Unfortunately CT examinations are costly and have the disadvantage of irradiation.

ERCP is the only single imaging technique with a specificity greater than 90 per cent in detecting pancreatic cancer[5,9]. In contrast, abnormalities of the common bile duct and/or the pancreatic duct are very rare in CUP, owing to the distance of the uncinate process from these structures. Therefore ERCP is of little or no use in detecting CUP.

Before the widespread availability of CT, angiography was considered a reliable method for detecting CUP[1]. Today, this diagnostic tool is reserved for the assessment of resectability in pancreatic cancer. None of the present patients with CUP exhibited pathological angiographic signs without the demonstration of a tumour in the uncinate process by CT. The proximity of the uncinate process to the mesenteric root, however, explains the high frequency of vascular involvement. This anatomical relationship also explains the significantly lower resection rate of CUP, compared with VPC. Resection of involved vascular segments was necessary in three of 12 resected patients. In the authors' opinion it is therefore necessary

Table 4 Survival according to Union Internacional Contra la Cancrum stage

	CUP		Median survival (months)	
Stage	Men	Women	CUP	VPC
I	–	–	–	19
II	3	1	9	12
III	8	7	6	8
IV	7	13	3·5	6
All stages			5	11*

CUP, carcinoma of the uncinate process; VPC, carcinoma of the ventral pancreatic head. *$P < 0{\cdot}05$ (VPC *versus* CUP, Student's *t* test) to know whether vascular infiltration is to be expected before starting a potentially dangerous pancreatic resection, even if performed by an experienced surgeon.

It is difficult to compare the outcome of patients with CUP in the present study with the findings from earlier series, as these included only small numbers of patients, but it seems that outcome has not improved despite better diagnostic methods. The mortality rate after pancreatic resection, however, has decreased significantly over the past 20 years[10].

The prognosis of patients suffering from CUP is worse than that for other forms of pancreatic cancer. From the present study, three important factors appear to be responsible for this phenomenon: (1) the lack of specific early symptoms especially of jaundice; (2) higher demands on imaging systems; and (3) early vascular involvement resulting in irresectability. The localization of pancreatic cancer in the uncinate process therefore represents a separate entity of its own. The diagnostic demands for proper preoperative assessment are high and require experience. Even smaller tumours (which are generally accompanied by a better prognosis) directly adjacent to the mesenteric root may be considered irresectable if vascular replacement is not considered. This may be a strenuous and risky addition to the planned operation if the surgeon is inexperienced in these procedures.

The surgical therapy of CUP should therefore be undertaken only in referral centres where pancreatic resection is performed frequently.

In conclusion, patients presenting with upper abdominal discomfort and a raised serum level of CA19-9 should undergo CT without delay to exclude a pancreatic neoplasm. Owing to the lack of accurate screening methods, the only way to improve the poor prognosis of patients with pancreatic carcinoma in the uncinate process appears to be the early application of currently available diagnostic tools and the constant improvement of surgical results along with the commitment to perform extended procedures including vascular replacement.

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Raised endothelin 1 levels in patients with colorectal liver metastases

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Background Endothelin 1 (ET-1), a vasoconstrictor peptide, has been implicated as a tumour growth stimulator and an angiogenesis factor.

Methods To assess the involvement of ET-1 in colorectal cancer, immunoelectron microscopy for ET-1 was performed in colorectal liver metastases and normal liver ($n = 6$). ET-1 plasma levels were measured by radioimmunoassay in patients with colorectal cancer, with ($n = 18$) and without ($n = 12$) liver metastases, and in controls ($n = 22$).

Results In normal liver, ET-1 was present in endothelial cells; in tumour, it was observed in endothelial cells, tumour cells and myofibroblasts. Mean(s.d.) plasma ET-1 levels were 2·75 (1·37) pg/ml in controls, 4·53(1·61) pg/ml in patients with colorectal liver metastases ($P = 0·001$) and 3·92(1·32) pg/ml in patients without metastases ($P = 0·02$).

Conclusion ET-1 was present in various cell types within colorectal liver metastases and raised levels were found in the plasma of patients with colorectal cancer. ET-1 may not only modulate tumour vascular tone but also act on tumour growth and angiogenesis, both locally and systemically.

The level of endothelin 1 (ET-1), a peptide with recognized vasoconstrictor properties, is known to be raised in the plasma of patients with a variety of conditions associated with vasospasm including pregnancy-induced hypertension, myocardial infarction and cardiogenic shock[1–3]. ET-1 plasma levels are also raised in patients with hepatocellular carcinoma[4].

In addition to its vasoconstrictor properties, ET-1 stimulates cellular proliferation *in vitro* in a variety of normal cell types including smooth muscle, fibroblasts, renal mesangial cells[5–7] and several tumour cell lines, including a number derived from colorectal cancers[8]. Histochemical analysis of different types of cancer, e.g. hepatocellular carcinoma[9], showed raised levels of ET-1 in tumour compared with normal tissue. Immunohistochemical analysis on primary colorectal cancer specimens demonstrated a heterogeneous distribution of ET-1 binding sites around tumour cell nests and associated vessels[10]. These findings suggest that ET-1 may perform a paracrine function in such tumours, in relation to both mitogenesis and blood supply.

To assess the importance of ET-1 in colorectal cancer, with particular emphasis on liver metastases, immunoelectron microscopy for ET-1 was performed on colorectal liver metastases and adjacent normal liver obtained at hepatectomy. Immunoelectron microscopy was chosen, as opposed to immunohistochemistry, so that the presence of ET-1 could be detected and also the cell types associated with it identified. In addition, plasma levels of ET-1 were measured in patients with colorectal cancer, with and without liver metastases, and compared with those in an age-and sex-matched control group.

Patients and methods

Pre-embedding immunohistochemistry for electron microscopy

Patients and tissue preparation. Six patients undergoing surgery for colorectal liver metastases were included in this study; five patients (age range 56-65 years) underwent right hemihepatectomy and one patient (aged 49 years) had segments VI and VII excised from the right liver lobe. Specimens were taken from metastatic tissue and from normal liver (at least 5 cm away from the tumour) and were fixed, within 30 min of excision, in 4 per cent paraformaldehyde and 0·25 per cent glutaraldehyde in 0·1 mol/l cacodylate buffer pH 7·3 for no less than 4–6 h at 4°C[11]. Tissue was then transferred to cacodylate buffer and stored overnight at 4°C.

Pre-embedding immunohistochemistry. For localization of ET-1, tissue was processed according to the peroxidase–anti-peroxidase (PAP) method of Sternberger[12], modified as reported previously[13,14]. Briefly, samples were exposed to 0·3 per cent hydrogen peroxide in 50 per cent methanol for 30 min (for blocking endogenous peroxidase activity), washed in 0·1 mol/l Tris buffer pH 7·4 (Tris), exposed to normal goat serum (Nordic Immunology, Tilberg, The Netherlands) diluted 1:40 in Tris containing 0·1 per cent sodium azide and 0·5 per cent bovine albumin (Sigma, Poole, UK) for 1·5 h and then rinsed in Tris. Samples were incubated for 48 h at 4°C with a rabbit antibody for ET-1 or eNOS (endothelial nitric oxide synthase) at a dilution of 1:1000 in Tris containing 0·1 per cent sodium azide and 0·5 per cent bovine albumin. The specimens were washed in Tris and exposed for 1·5 h to goat antirabbit immunoglobulin G serum (Cappel Labs, West Chester, Pennsylvania, USA) diluted 1:40 in Tris containing 0·1 per cent sodium azide and 0·5 per cent bovine albumin, washed in Tris, and incubated for 3 h with rabbit PAP complex (Dakopatts, Glostrup, Denmark) diluted 1:60 in Tris. After exposure to 3′,3′-diaminobenzidine (Sigma) and hydrogen peroxide, the specimens were washed in Tris and then postfixed with 2·5 per cent glutaraldehyde in cacodylated buffer (pH 7·4) overnight. The specimens were washed with phosphate buffer, postfixed in 1 per cent osmium tetroxide, dehydrated through a graded series of ethanol and propylene oxide and then embedded in epoxy resin (Durcupan A/M; Fluka

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HE, Switzerland) as described previously[11], for transmission electron microscopy. Semithin sections for preliminary electron microscopy analysis were stained with 1 per cent toluidene blue and examined under a Ziess light microscope (Carl Zeiss, Jena, Germany). Ultrathin sections were stained with uranyl acetate and lead citrate, and investigated using a Jeol TEM-1010 microscope (Japan).

Assays for endothelin 1 and thrombomodulin

Blood collection. Three groups of patients were studied: controls ($n = 22$), patients with primary colorectal cancer without liver metastases ($n = 12$) and patients with liver metastases ($n = 18$). Patients with hypertension, renal failure, heart disease, pre-existing liver disease or Raynaud's phenomenon, which are independently associated with raised ET-1 levels, were excluded.

All patients had a fasting venous specimen taken before surgery; blood for thrombomodulin (TM) and ET-1 assay was collected into precooled bottles containing trisodium citrate 0·109 mol/l and ethylenediamine tetra-acetic acid 9 mmol/l respectively. TM was used as a marker of endothelial damage, as ET-1 levels are raised in the presence of endothelial trauma. The specimens were centrifuged at 1000*g* for 15 min at 4°C and the plasma was frozen at − 70°C within 1 h of collection.

Endothelin 1 radioimmunoassay. Plasma ET-1 was measured by radioimmunoassay (Nichols Institute Diagnostics, Saffron Walden, UK) according to the manufacturer's instructions. ET-1 concentrations were calculated by plotting the percentage bound against log concentrations of known standards.

Thrombomodulin assay. Plasma TM was measured by an enzyme-linked immunosorbent assay (Diagnostica Stago, Asnieres, France) according to the manufacturer's instructions. Plates were read at 492 nm and a standard curve plotted using absorbance against log concentration.

Statistical analysis. Values are mean(s.d.). The significance of the differences was calculated using paired and unpaired *t* tests. $P < 0·05$ was considered significant. Clinical information, including carcinoembryonic antigen (CEA) level, tumour load and results of liver function tests, were recorded for each patient.

Results

Immunoelectron microscopy for endothelin 1

Normal liver. Within the portal tracts, the branches of the hepatic artery and vein were lined by a single layer of endothelial cells. Only a few endothelial cells showed immunopositivity for ET-1 and, when present, the level of labelling was low compared with that in similar areas of the tumour.

Liver metastases. The colorectal liver metastases had a markedly different morphological structure. A heterogeneous distribution of blood vessels was observed throughout the tumours, with the central portions showing areas lacking any differentiation or cellular boundaries, as described previously[15]. The tumour blood vessels appeared uniformly primitive lacking both a continuous smooth muscle coat and any evidence of innervation (*Fig. 1*). The only exception to this pattern was at the junction with the adjacent liver, where presumably normal blood vessels were being incorporated into the tumour and as such still retained a degree of their normal structure. The tumour appeared markedly less vascular than the surrounding tissue. In addition, a large number of myofibroblasts and

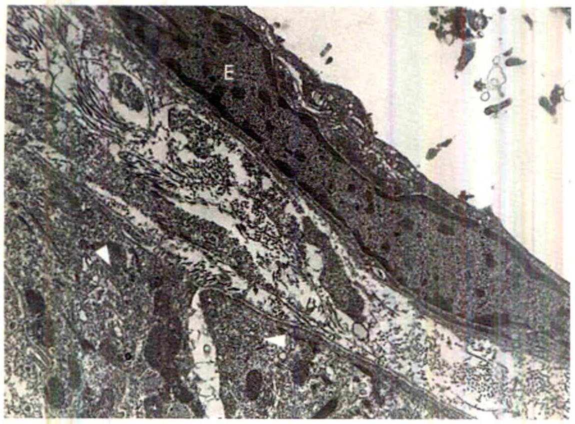

Fig. 1 Electron micrograph of a blood vessel within a liver metastasis, showing typical endothelin 1 immunostaining of an endothelial cell (E). Note the adjacent unlabelled cells (arrowheads) (original magnification × 10 000)

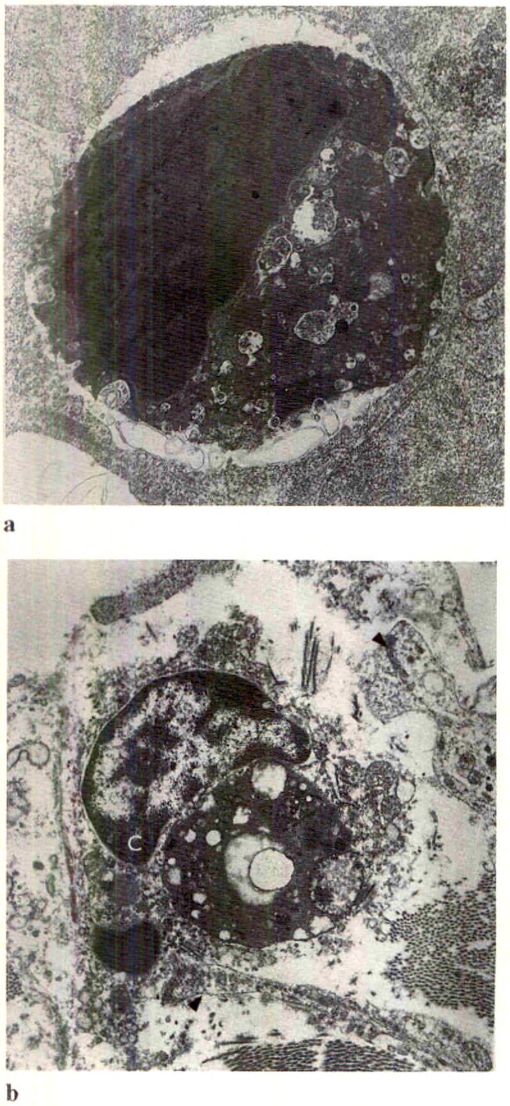

Fig. 2 a Endothelin 1-positive labelled tumour cell in metastatic tissue (original magnification × 20 000). **b** Cancer cell (C) stained positive for endothelin 1. Note the adjacent unlabelled cells (arrowheads) (original magnification × 13 000)

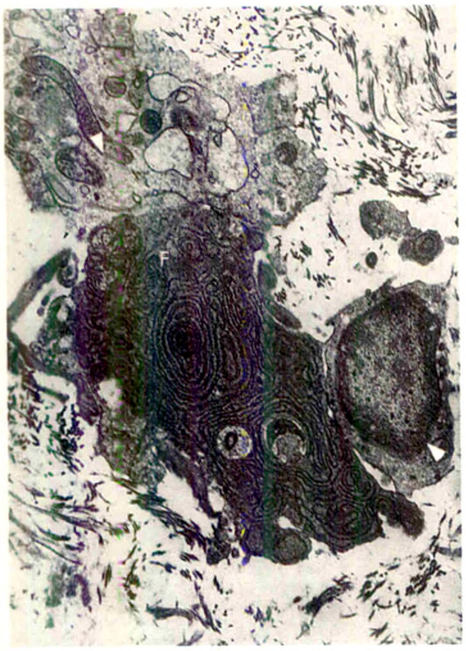

Fig. 3 Endothelin 1-positive labelled fibroblast (F) within a liver metastasis. Note the adjacent unlabelled cells (arrowheads) (original magnification × 10 000)

connective tissue were found around the tumour cell nests. The distribution of ET-1 was very different from that in normal liver with ET-1 staining strongly positive within the tumour cells (*Fig. 2*) and the surrounding fibroblasts (*Fig. 3*). In addition there was an increase in the percentage of the population of ET-1-positive endothelial cells in these tumours.

Plasma levels of endothelin 1 and thrombomodulin

Mean(s.d.) plasma level of ET-1 in the control group (age range 42–82 (mean 59·5) years; eight women and 14 men) was 2·75(1·37) pg/ml. In patients with colorectal cancer without metastases (age range 55–77 (mean 64·2) years; seven women and five men) it was 3·92(1·32) pg/ml and in those with liver metastases (age range 46–75 (mean 58·9) years; three women and 15 men) 4·53(1·61) pg/ml (*Fig. 4*). There was a significant difference between the patients with cancer and the control group ($P = 0{\cdot}001$ and $P = 0{\cdot}02$ for patients with metastases and primary cancer respectively) whilst there was no significant difference between the two groups of patients with cancer. No correlation was found between ET-1 level and liver function or serum CEA, but ET-1 concentration appeared to rise with increasing size of the liver metastases.

The mean(s.d.) TM level in the control group (53·8 (15·8) ng/ml) was not significantly different from that in the primary colorectal cancer group (52·0(11·8) ng/ml) or metastases group (64·3(22·6) ng/ml) (*Fig. 5*).

Discussion

ET-1 is known to be produced predominantly by vascular endothelial cells[16], with the precursor peptide processed to the mature form inside the cell. As well as having a local

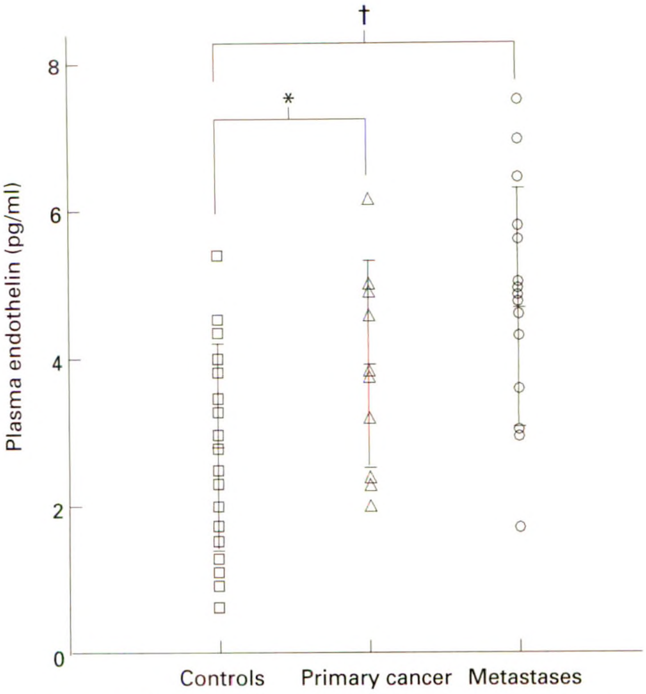

Fig. 4 Levels of endothelin-1 in plasma from patients with or without colorectal cancer. Individual values are shown for controls ($n = 22$), patients with primary colorectal cancer ($n = 12$) and patients with previously detected primary colorectal cancer who have now developed liver metastases ($n = 18$). Bars are mean(s.d.). $^*P = 0{\cdot}02$, $^\dagger P = 0{\cdot}001$ (unpaired *t* test)

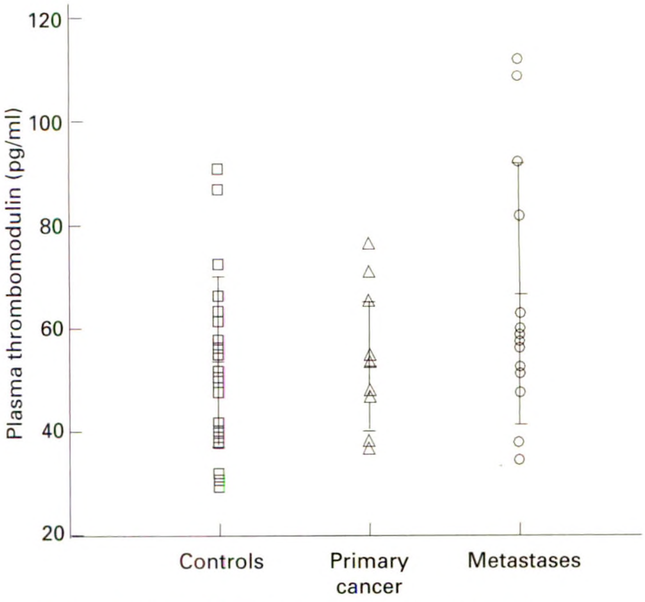

Fig. 5 Levels of thrombomodulin detected in plasma from patients with or without colorectal cancer. Individual values are shown for controls in ($n = 22$), patients with primary colorectal cancer ($n = 12$) and patients with previously detected primary colorectal cancer who have now developed liver metastases ($n = 18$). Bars are mean(s.d.). There were no significant differences between groups (unpaired *t* test)

effect, a systemic action is suggested by its presence in the plasma of healthy individuals. The results of this study suggest that a number of different cell types within colorectal liver metastases produce ET-1 with a concomitant rise in plasma levels.

The presence of ET-1 within the endothelium of normal hepatic vessels, demonstrated by immunoelectron microscopy, is in keeping with previous findings in other vascular beds, e.g. skin and coronary circulation[17,18], and conforms to the suggested function of ET-1 as an endothelial cell-derived vasoconstrictor. ET-1 is known to influence normal hepatocytes, bile flow and hepatic arterial and portal venous blood flow, with the liver also being one of the major sites of endothelin clearance[19,20]. It is not, however, a major source of ET-1 as illustrated by its absence in the remainder of the liver in this study.

Studies involving tissue culture systems have shown that a variety of tumour cell lines including colonic adenocarcinomas produce ET-1, which is then detectable in the culture medium[8]. Such findings are mirrored *in vivo* with Inagaki *et al.*[10] showing increased amounts of ET-1 in primary colonic cancers and increased levels of ET-1 receptors on surrounding cells including myofibroblasts.

A possible explanation for these findings may be found outside the commonly accepted role of endothelins as vasoconstrictors. ET-1 is known to be mitogenic for a variety of cell types including vascular smooth muscle, renal mesangial cells and colonic cancers[5-8]. Shichiri and colleagues[8] not only demonstrated that a variety of epithelial human cancer cell lines produced ET-1 but also that the peptide caused a rise in mitogenesis in a dose-dependent manner. Given the above findings in colonic cancers, ET-1 may have a paracrine or autocrine function in regard to tumour growth. In addition to its mitogenic effect, ET-1 is also directly and indirectly angiogenic, a process of particular importance in tumour growth. ET-1 is a direct endothelial cell mitogen and indirectly stimulates angiogenesis by causing monocytes to produce interleukin 8, a potent angiogenic agent[21,22].

ET-1 was present in large amounts within the cytoplasm of tumour cells and surrounding myofibroblasts throughout all the specimens examined. This raised expression suggests that ET-1 may be produced by both tumour cells and surrounding associated cell types and may therefore play a part in tumour growth regulation. The increased expression of ET-1 in tumour vessel endothelial cells compared with normal hepatic vasculature, demonstrated using immunospecific peroxidase, may suggest an upregulation of its vasoconstrictor effect in addition to growth stimulation.

The increase in production of ET-1 by colonic cancers is mirrored in the plasma of such patients, suggesting a systemic as well as a local function. It is recognized that primary tumours may influence not only their own growth but also that of distant metastases[23]. This appears to be achieved via the release of a variety of regulatory angiogenic and mitogenic substances[24]. ET-1 may perform a function in this regard with increased production perhaps leading to greater metastatic growth. The use of ET-1 as a tumour marker, however, is unlikely to be of any clinical use given the degree of overlap in the three groups of patients studied and the number of other conditions independently associated with an increased ET-1 level. Systemic levels of ET-1 are raised in a variety of pathological conditions associated with vasospasm including pregnancy-induced hypertension, cardiogenic shock and myocardial infarction[1-3].

It has been known for some time that the presence of liver metastases is associated with subtle alterations in hepatic blood flow[25]. The hepatic perfusion index (HPI), which is the ratio of hepatic arterial flow to total liver blood flow, is raised in such patients, even at a micrometastatic stage[26]. This phenomenon is caused by splanchnic vasoconstriction and a subsequent reduction in portal inflow. Animal studies suggest this is due to the presence of a circulating vasoconstrictor which is not one of the commonly identified physiological vasoactive agents[27]. Clinical studies looking at patients with liver metastases suggest that the HPI may be used as an accurate predictor of the presence of hepatic metastases[28]. Given that ET-1 is a potent vasoconstrictor with marked effects on the splanchnic bed and is produced by colorectal cancers, it might have a role in this phenomenon. However, in this study there was no significant difference in the plasma levels of ET-1 between patients with and without liver metastases.

In conclusion, this study demonstrated that in colorectal liver metastases endothelial cells contain raised levels of ET-1, and ET-1 expression is upregulated in both tumour cells and associated myofibroblasts. An increased level of ET-1 is also found in the plasma of patients with colorectal cancer with and without liver metastases. Whether or not ET-1 regulates tumour growth locally and systemically and whether its increased levels indicate progression of disease remains to be determined by future studies.

Acknowledgements

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Short note

Carotid endarterectomy is safe in selected elderly patients

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The incidence of thromboembolic stroke increases with age, but 90 per cent of family doctors remain less likely to refer patients aged 70 years or more for carotid endarterectomy (CEA)[1] because it is perceived that they have a higher operative risk. This study is a prospective audit of the risk of death and/or stroke in elderly patients following CEA.

Patients and methods

A prospective, consecutive audit of 235 CEAs in patients aged 70 years or more (median 75 (range 70–88) years) was performed between January 1992 and July 1997. All patients had an ipsilateral stenosis of 70 per cent or greater; one-third had a contralateral occlusion or severe stenosis. During the same interval, 317 CEAs were performed in patients aged less than 70 years. Endarterectomy was performed under normotensive, normocarbic general anaesthesia with systemic heparinization, and routine shunting and patching. Transcranial Doppler (TCD) monitoring and completion angioscopy were introduced in 1992[2] and supplemented by routine postoperative TCD monitoring in October 1995[3].

Results

The death/disabling stroke rate in patients aged 70 years or more was 2·6 per cent (*Table 1*). Whilst the rate of death/any stroke was 3·8 per cent. The commonest single cause of morbidity was postoperative carotid thrombosis (five of nine patients). However, following implementation of a full perioperative monitoring programme in 97 elderly patients have now undergone carotid surgery without incurring an operative stroke (*Table 1*).

Table 1 Perioperative death and stroke rates following carotid endarterectomy

Age (years)	No. of CEAs	Death/disabling stroke	Death/any stroke
Overall			
40–69	317	8 (2·5)	14 (4·4)
70–90	235	6 (2·6)	9 (3·8)
Since introduction of full perioperative monitoring			
40–69	121	1 (0·8)	3 (2·5)
70–90	97	0 (0)	0 (0)

Values in parentheses are percentages. CEA, carotid endarterectomy

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Discussion

This study suggests that CEA can be performed safely in selected elderly patients and that age alone should not be an automatic bar to consideration for surgery. The authors cannot, however, comment on selection of individual elderly patients as many may not have been referred to them. During the study, the main exclusion criteria for operation were a concurrent illness giving an anticipated survival of less than 2 years, dementia or an inability to maintain independent living. The final decision with regard to medical fitness for operation was made by a consultant anaesthetist.

It has been suggested previously that patients at highest risk of perioperative stroke are more susceptible to the effects of microembolization or impaired perfusion so that the margin for technical error is reduced[4]. Over the past 5 years the authors have implemented a policy of perioperative monitoring and quality control with the specific aim of identifying and correcting inadvertent technical error before it can cause harm. The fact that no elderly patient has suffered an operative stroke following full implementation of this policy suggests that such an approach may be an alternative to excluding elderly or other high-risk patients from surgery.

Although it is unarguable that long-term survival is reduced in the elderly patient, age alone should not be a reason to deny surgery which could prevent death or disabling stroke.

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Trials and tribulations of vascular surgical benchmarking

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Background Benchmarking is a new tool to assess the efficiency of different hospitals. Classification of operations using healthcare resource groups (HRGs) is related to parameters including number of cases, length of stay (LOS) and age profile.

Methods A National Comparative Database was used to compare three hospitals. Analysis was confined to the major HRGs involved with vascular/venous surgery.

Results For high-volume low-complexity varicose vein surgery, all three hospitals had similar numbers of patients and LOS. In contrast, the LOS for routine vascular operations in hospital A was double that in hospital B (16·3 *versus* 7·4 days). Hospital A had three times as many patients classified as 'other – peripheral vascular disease' as hospital C and six times as many as hospital B (329, 49 and 111 for hospitals A, B and C respectively). LOS following major amputation in hospitals A and C was nearly double that in hospital B (32·4, 18·3 and 33·6 days for hospitals A, B and C respectively).

Conclusion There were a number of significant variations between the three hospitals during the 9-month interval. Explanations included the methods of coding, local facilities including availability of rehabilitation beds and difference in the patients' age profiles. Benchmarking in its present format reveals a number of variations which may not necessarily reflect real differences in clinical performance.

Attempts to classify procedures with a view to comparison of the efficiency of different hospitals began in the USA in the late 1970s with the advent of diagnosis related groups (DRGs)[1]. These were, however, thought to be too detailed[2] for routine use in the UK, and hence were adapted to create a simpler version, healthcare resource groups (HRGs). HRGs are used to identify 'groups of patients expected to consume similar amounts of health care resources'.

Following modification, version 2 has been in use since 1992[3]. HRGs are now being used to 'benchmark', i.e. to compare clinical efficiency between different hospitals nationally[4]. Version 3 is nearing completion with a variety of modifications, allowing a more accurate allocation to clinical vascular practice. Every acute hospital will cost all surgical specialties using HRGs for the 1997–1998 contract year for both elective and emergency surgery.

One of the criticisms is that DRGs and HRGs were used initially to define complexity, but that they are increasingly based on length of stay (LOS), which forms the largest part of the cost of a hospital admission.

HRGs can be assigned automatically using the 'Healthcare Resource Grouper' (National Case Mix Office, Winchester, UK). This software programme uses a number of different criteria based on rank to allocate a particular HRG. The main criterion is whether any significant procedure has taken place. Primary and secondary diagnoses together with complications or comorbidity are included, but only if no procedure is recorded. Other factors included age in association with the primary diagnosis, and admission specialty.

In view of the increasing importance of HRGs, especially in contracting arrangements, currently collated data have been used to compare and contrast the performance of three major vascular centres.

Materials and methods

Data collected for use in a National Comparative Database (CHKS, 1996) was used with permission of CHKS and a nominated representative of each vascular unit (authors). Data analysis has been confined to the major HRGs concerned with vascular/venous surgery (*Table 1*). Methods and/or difficulties of coding were also noted.

Individual hospitals have not been identified and some comments will be left as observations rather than specific points, to help preserve anonymity.

The data were not modified or verified beyond that supplied from the comparative database. A 9-month interval from April to December 1995 was studied.

Results

There were no differences between hospitals in high-volume, low-complexity varicose vein surgery (e44); patients in this group are predominantly treated as day cases. Varicose vein surgery is largely unaffected by any differences in local facilities and social circumstances. Furthermore, it is protected from coding errors as a single code is used to cover all varicose vein operations (*Table 1*).

In contrast, there was a marked discrepancy in LOS between hospital A, and hospitals B and C in relation to e41 (emergency or complex vascular surgery) and e42 (routine vascular surgery). Furthermore, while hospital B had a comparatively short LOS following major

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Table 1 Numbers of patients and length of stay in hospital in vascular healthcare resource groups

	e41		e42		e44		e48		e45		e46		e50	
Hospital	*n*	LOS (days)	*n*	LOS (days)	*n*	LOS (days)	*n*	LOS (days)	*n*	LOS (days)	*n*	LOS (days)	*n*	LOS (days)
A	15	16·9	203	16·3	241	4·9	12	32·4	21	4·9	132	2·9	329	4·2
B	23	9·0	177	7·4	252	1·0	40	18·3	58	2·1	249	2·0	49	3·2
C	20	8·9	202	9·4	277	1·3	30	33·6	59	2·9	280	2·4	111	4·4

e41, Complex/emergency vascular operations; e42, routine vascular operations; e44, varicose veins; e45, interventional radiology; e46, diagnostic radiology; e48, major amputations; e50, 'other – peripheral vascular disease'. LOS, length of stay

amputations (e48), considerably more amputations were performed there than in either hospital A or C, which apparently took almost twice as long to discharge the same type of patient.

For other groups, coding difficulties or indeed errors appeared to be more frequent. Hospital A had nearly seven times as many patients grouped into e50 than hospital B and nearly three times as many as hospital C. At least part of this major difference was accounted for by the variation in coding between e45 and e46. Hospital A had only half the activity in these two HRGs compared with either hospital B or C. A large number (approximately 200) of the patients in e50 were assigned incorrectly and should have been categorized in e45 or e46. This is because of the lack of a direct 'feed' from the computer systems in the radiology department with those operating the HRG software. This work is now carried out manually to correct the problem.

Discussion

For varicose vein surgery, there is only one HRG code, so coding errors are rare; most patients are treated as a day case and rehabilitation deficiencies or social difficulties are not usually applicable.

By contrast the discrepancies between the three institutions in the e50 HRG reflect the major coding differences between the hospitals; the majority of these patients really belong to a different HRG. Differing coding procedures for emergency and elective cases also exist; some are based on the time of operation and others rely on the nature of admission (i.e. elective or emergency), retaining that classification even if the subsequent procedure is performed on an elective operating list during the same admission.

There are many factors which influence the stay in hospital for a certain procedure. Clinical practice can only suggest when admission and discharge are appropriate for a particular patient. The provision of physiotherapy, occupational therapy and social workers can have a major influence on the ability to perform care assessments and home visits before discharge as required under the Community Care Act. The ability to discharge otherwise fit patients to local convalescent or general practitioner-managed community beds is also variable. Some 'acute' surgical beds are undoubtedly used for convalescence in the absence of other available facilities.

HRGs will shortly be used as part of the contracting process. It is important therefore that the information used in these comparative analyses is accurate. Any major differences need to be studied to ensure that inappropriate coding, or insufficient local resources outside the control of the clinician, do not allow an unfavourable and inappropriate conclusion towards a particular HRG.

Reimbursement based on HRGs alone is susceptible to inadequate resourcing for patients who have the same operation but for different indications. Gupta and Veith[5] found that reimbursement almost matched costs when a femoropopliteal graft was done for claudication, but was often insufficient when the same operation was done for limb salvage.

Munoz *et al.*[6] examined 1169 patients having peripheral vascular surgery to determine if the cost per DRG could be predicted. Four clinical parameters were used: (1) emergency admission, (2) surgical intensive care unit admission, (3) infusion of plasma product or (4) blood transfusion. Patients with these parameters had significantly higher costs than patients in the same DRG without these factors.

Similarly, the source of referral is important. Patients referred by a physician were shown to incur a 146·5 per cent higher costing than those admitted directly to a surgeon[7]. Important contributory factors included more severe illness, increased diagnostic costs and delays in diagnosis or treatment.

Rhodes *et al.*[8] found that the duration of hospital stay for above-knee popliteal, below-knee popliteal, and tibioperoneal artery reconstructions was significantly different ($P < 0{\cdot}005$). More distal vascular procedures were also associated with higher morbidity and mortality rates. There were major differences between the patients treated by different surgeons with respect to age, previous ipsilateral surgery, crural bypass and co-morbidity. 'The most highly qualified surgeons dealt with the sickest patients.'

In the future, version 3 HRGs may remedy at least some of the coding difficulties highlighted in version 2. In addition, healthcare benefit groups are also being developed which will be used to stratify patients by severity of illness and co-morbidity.

It is essential that clinicians are actively involved in the verification of HRG coding to ensure that their workload and efficiency are accurately represented. Astute clinicians may evaluate any restrictions to rapid admission and discharge which will unfavourably influence their patients' hospital stay.

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Surgical workshop

Cryopreserved aortic homografts for patients who need simultaneous aortic and gastrointestinal surgery

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Patients with intra-abdominal infection and a simultaneous vascular emergency are usually treated by extra-anatomic bypass grafting or *in situ* reconstruction with a prosthetic graft. Subsequent reinfection is common, leading to substantial mortality and morbidity rates[1]. Cryopreserved aortic homografts, being resistant to infection[2], allow safe *in situ* vascular repair and simultaneous surgery for the intra-abdominal infection.

Surgical technique

Between 1994 and 1996, six patients of mean(s.d.) age 60(12) years had surgery for simultaneous aortic and gastrointestinal problems. One patient had an aortobi-iliac bifurcation graft with resection of the left colon for intestinal ischaemia 2 years previously. He presented with recurrent rectal bleeding due to a fistula between the rectal stump and the prosthetic graft (*Fig. 1*). The prosthesis was replaced by an aortic homograft and the upper rectal stump closed. The second patient had an aortointestinal fistula involving an aortic bifurcation prosthesis penetrating the small intestine. A homograft was implanted and three segments of small intestine were resected. The third patient had perforated sigmoid diverticulitis covering an aortic aneurysm. The sigmoid colon was resected and a colostomy performed. The aneurysm was replaced by a homograft. The fourth patient had a ruptured infrarenal aortic aneurysm and ischaemic necrosis of the ascending colon. The right colon was resected leaving an ileostomy and transverse colostomy, and the aneurysm was replaced by a homograft. The final two patients developed aortoenteric fistulas originating from an anastomotic aneurysm of the prosthetic graft. Both were replaced by homografts. All vascular anastomoses were performed end to end using polypropylene sutures.

One patient died on the seventh postoperative day from a sudden cardiac event. Otherwise there was no perioperative morbidity including sepsis, organ failure or vascular problems. Mean(s.d.) hospital stay was 28(11) (range 14–35) days. Intravenous antibiotics were continued for 6 weeks. At mean(s.d.) follow-up of 16(6) (range 9–25) months all patients underwent computed tomography or magnetic resonance imaging without any evidence of reinfection, suture line complications or homograft stenosis.

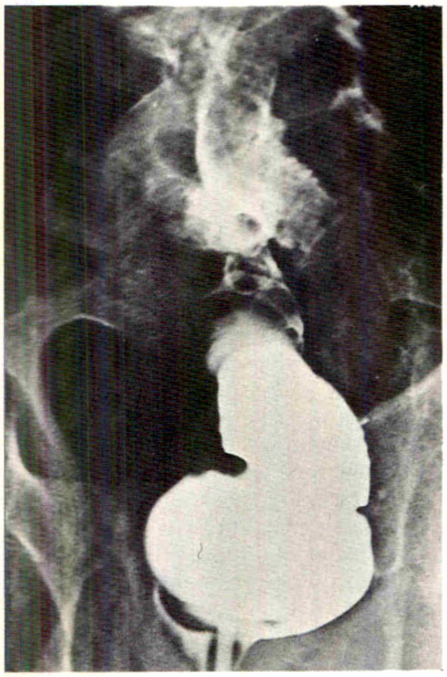

Fig. 1 Aortoenteric fistula from the upper rectal stump to an infrarenal bifurcation prosthesis leading to recurrent rectal bleeding

Discussion

Favourable results with cryopreserved homograft heart valves in the treatment of aortic valve endocarditis stimulated the use of cryopreserved aortic homografts for *in situ* repair of major vascular infections[2,3]. Standard extra-anatomic bypass or prosthetic *in situ* techniques in this situation are known to have high rates of reinfection, suture line dehiscence and requirement for long-term antibiotic treatment[1]. The use of homograft allowed a one-stage *in situ* repair in conjunction with limited antibiotic treatment for 6 weeks, a policy adopted from heart valve homograft surgery.

Although the long-term fate of cryopreserved aortic homografts is unknown[2], early deaths and morbidity[1] are the major concerns in the surgical treatment of aortic graft infections. The relatively short hospital stay and the absence of reinfection or anastomotic aneurysms in this series suggest that one-stage *in situ* homograft repair can be used safely when simultaneous aortic and gastrointestinal surgery is necessary.

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Ruptured hepatocellular carcinoma as a complication of transarterial oily chemoembolization

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Background Transarterial oily chemoembolization (TOCE) is frequently employed as a non-operative treatment for hepatocellular carcinoma (HCC). Serious complications of TOCE are well known but ruptured HCC as a fatal complication of TOCE has not been reported previously.

Methods A retrospective study was performed on all patients who received TOCE for treatment of HCC from January 1989 to October 1996; the complication of ruptured HCC within 2 weeks from the procedure was recorded.

Results During the study period, 391 patients received a total of 1443 sessions of TOCE (mean 3·7 sessions per patient) for the treatment of HCC, with an overall median survival of 10·4 months. Six patients developed ruptured tumour within 2 weeks after TOCE, resulting in an overall incidence of 1·5 per cent per patient or 0·4 per cent per procedure. All except one patient died 1–25 days after tumour rupture. Factors common to these six patients included: (1) male sex; (2) large tumour size (range 8–17 cm in diameter); (3) tumour located in the right lobe of the liver; (4) tumour ruptured after the first session of TOCE; and (5) TOCE performed as primary treatment without previous hepatic resection.

Conclusion Ruptured HCC is a serious complication of TOCE although the incidence is low. It occurred predominantly in men after the first session of TOCE for a large irresectable tumour of the right lobe.

Hepatocellular carcinoma (HCC) is one of the commonest cancers encountered in Asian countries and the incidence is increasing in the Western world. In China, HCC claims about 100 000 lives annually[1]. As only about 20 per cent of the tumours are considered resectable on presentation and a high incidence of postresectional recurrence has been observed[2–4], non-resectional therapies are frequently employed, the commonest of which is transarterial oily chemoembolization (TOCE). Although satisfactory survival results have been reported, complications of TOCE with significant morbidity are well known and adversely affect the outcome of patients[5]. Rupture is a catastrophic complication of HCC and has a high mortality rate. In the majority of cases, rupture of HCC occurs spontaneously although a history of minor trauma may be associated occasionally[6,7]. As far as the authors are aware, rupture of HCC as a fatal complication of TOCE has not been reported in the English literature.

Patients and methods

A retrospective study was performed on all patients who received TOCE as a primary treatment for irresectable HCC or as treatment for residual and recurrent disease after surgical resection from January 1989 to October 1996 in the Department of Surgery at Queen Mary Hospital, Hong Kong. Twenty-six patients who received systemic chemotherapy and TOCE after curative resection of HCC as part of a randomized trial of postoperative adjuvant chemotherapy during the study period were excluded from the study. TOCE was performed in the Department of Diagnostic Radiology, Queen Mary Hospital, Hong Kong.

Some 10 ml of Lipiodol (Lipiodol Ultrafluide; Laboratoire Guerbet, Aulnay-sous-Bois, France) was mixed with 10 mg of cisplatin by the pumping method into a milky emulsion of 20 ml. A torque-controlled 5-Fr catheter was inserted via a femoral artery and placed into a branch of the hepatic artery supplying the HCC or into the proper hepatic artery distal to the gastroduodenal artery if both lobes of liver were involved by tumour. Between 4 and 40 ml of the emulsion were infused into the liver depending on the size of the HCC. Light embolization of the feeding artery was then performed with small gelfoam pellets, which were prepared by cutting a gelfoam block into small cubes of approximately 1 mm in size. Injection of gelfoam was stopped when blood flow in the artery supplying the tumour slowed down but before occlusion occurred.

All patients were kept in bed for 12 h after the procedure and were prescribed oral antibiotic prophylaxis for 3 days and H_2-receptor antagonists for 1 week. The procedure was repeated at regular intervals for between 1·5 and 3 months. The details of all patients who developed rupture of HCC within 2 weeks of the procedure were recorded. Rupture of the HCC was diagnosed when the patient complained of abdominal pain with associated haemodynamic changes, a drop in haemoglobin concentration of 2 g/dl or more, and when haemoperitoneum was demonstrated by abdominal paracentesis. The clinical parameters of patients who developed ruptured HCC were compared with those of other patients without the complication.

Results

During the study period 391 patients received a total of 1443 sessions of TOCE (mean 3·7 sessions per patient). Some 333 patients (85·2 per cent) received TOCE as primary treatment for irresectable disease, and 58 (14·8 per cent) had TOCE because of recurrence or residual disease after resection. There were 337 men and 54 women. Mean tumour diameter was 7·5 cm before treatment. Median survival was 10·4 months and 132

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patients were still alive with a median follow-up of 14 months at the time of preparation of the manuscript.

During the study period, six patients developed ruptured HCC 1–14 (median 2) days after the first session of TOCE, resulting in an overall incidence of 1·5 per cent per patient or 0·4 per cent per procedure. The size of the tumours that ruptured ranged from 8 to 17 (median 13·5) cm in diameter. Significant haemodynamic changes were observed in all patients; mean transfusion requirement was 2·0 (range 0–5) units. Five of the six patients died 1–25 (median 13) days after tumour rupture. Bleeding was the direct cause of death in two patients who died soon after rupture of the tumour. The cause of death was liver failure in the other three patients, although they survived the initial haemodynamic insult. One patient who experienced a minor rupture of HCC after TOCE was still alive at 6 months of follow-up. He received two further courses of TOCE and had a satisfactory response to treatment. No interventional procedure such as transarterial embolization, ligation of hepatic artery or surgical haemostasis was performed for these patients.

The clinical features of the six patients who developed ruptured HCC after TOCE are shown in *Table 1*. When compared with patients who did not have ruptured tumour after TOCE, the complication occurred predominantly after the first course of treatment in men who received TOCE as the primary treatment for large irresectable tumours located in the right lobe of the liver, although the difference was not statistically significant, probably because of the small number of patients.

Discussion

Although HCC is more prevalent in Asia and sub-Saharan Africa[8], it is a common global disease. The prognosis without treatment is poor, with a median survival of only 1·6 months[9]. Non-resectional therapies including TOCE play an essential role in the treatment of a large number of patients with irresectable or recurrent HCC. TOCE is a combination of targeted chemotherapy and arterial embolization to produce chemotherapeutic and ischaemic effects on the hepatoma. Yamada *et al.*[10] and others[11–17] have reported that the 1–5-year survival rates of patients with irresectable HCC after TOCE ranged from 51 to 6 per cent. Contraindications to TOCE include main portal vein thrombosis or obstruction by tumour, marked arteriovenous shunting to the portal or hepatic vein, and poor liver function. For the safety of TOCE therapy, it is important for clinicians who prescribe and for patients who undergo the procedure to understand the major complications involved and their predisposing factors. Complications of TOCE resulting in significant morbidity are well known and a treatment-related mortality rate of 4·1 per cent has been reported[5]. Fever, abdominal pain, ileus, nausea and vomiting after TOCE are commonly seen but usually subside within days. Chemotherapeutic and embolizing agents may cause chemical cholecystitis, pancreatitis, gastric and duodenal erosion, ulceration or necrosis if they are injected into these organs inadvertently. Infection of the necrotic tumour resulting in liver abscess and even serious sepsis have been reported[18,19]. Liver failure is a serious complication of TOCE and may result in death in patients with underlying advanced cirrhosis. Bile duct injury resulting in secondary sclerosing cholangitis[20], bile duct necrosis and biloma[21] have also been reported.

Table 1 Clinical features of patients who developed ruptured hepatocellular carcinoma after transarterial oily chemoembolization (group 1) and those without the complication (group 2)

	Group 1	Group 2
No. of patients	6	385
Sex ratio (M:F)	6:0	331:54
Age (years)*	55·7(5·1)	55·5(0·7)
Serum albumin (g/l)*	34·5(1·5)	39·5(0·3)
Serum total bilirubin (μmol/l)*	25·2(7·3)	18·0(0·7)
Aspartate aminotransferase (units/l)*	118·5(17·3)	95·1(4·6)
Haemoglobin (g/dl)*	11·3(0·5)	12·9(0·1)
Prothrombin time (s)*	13·2(0·3)	12·3(0·1)
Tumour diameter (cm)*	13·0(1·6)	7·5(0·3)
Primary treatment for irresectable disease	6	327
Location of main tumour at right lobe of liver	6	262
Sessions of treatment*	1·3(0·3)	3·7(0·2)
Median survival (months)	0·4	10·5

*Values are mean (s.e.m.)

Rupture is probably the most catastrophic complication of HCC. There is a distinct geographical difference in the reported incidence of this complication, ranging from over 10 per cent in Asian countries[22,23] to less than 3 per cent in the UK[24,25]. Rupture of HCC as a complication of TOCE has not, to the authors' knowledge, been reported in the English literature. As observed in the six patients who developed the complication in the present series, the prognosis is extremely poor: only one patient survived for more than 1 month. When compared with patients who did not develop the complication and who had a median survival of more than 10 months, the complication of rupture of HCC after TOCE adversely affected the survival.

The mechanism of rupture of HCC after TOCE is unclear. It can be postulated to be related to tumour necrosis and increased pressure inside the friable tumour after TOCE. These changes are expected to be maximal in a large tumour undergoing the first session of treatment. The tumour may then rupture or split the overlying non-tumorous liver[26] with or without trivial trauma including diaphragmatic movement on the right lobe of the liver[27]. In addition, large tumours are considered to be at increased risk of rupture as they are more likely to contact the liver surface and to have an increased extent of extrahepatic protrusion[28]. The mechanism of rupture may also be related to vascular injury secondary to chemoembolization. Development of acute necrotizing angiitis with resultant infiltration of inflammatory cells and thickening of the arterial wall has been reported in arteries embolized with gelatin sponge particles[29,30]; the arterial wall becomes fragile because of inflammatory and reparative changes. Aso *et al.*[31] reported on five patients who developed multiple intrahepatic aneurysms after transcatheter arterial embolization. It can be speculated, therefore, that vascular damage occurring in the pathological vessels of the hepatoma after TOCE may result in bleeding into the tumour, which subsequently ruptures. However, further reports and studies are required to delineate the predisposing factors and mechanism of rupture of HCC after TOCE.

Management of patients with rupture of HCC following TOCE is difficult as they have already been diagnosed as having inoperable large tumours and impaired liver function. Two patients deteriorated rapidly and died soon after development of the complication before any intervention could be performed. Three other patients developed liver failure and died within 1 month, although they survived the initial haemodynamic insult without any interventional procedure.

In summary, ruptured hepatoma is a serious complication of TOCE, although the incidence is low. It occurs predominantly in men after the first session of TOCE for large irresectable HCC of the right lobe.

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Improved survival in patients with rectal cancer: a population-based register study

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Background Between 1985 and 1989, only one centre in Sweden combined preoperative radiotherapy with total mesorectal excision (TME) in the primary treatment of rectal cancer. The aim of this study was to investigate whether this change in primary treatment had an impact on the outcome.

Method The survival rate of 94 262 patients with colorectal cancer from the total Swedish population between 1960 and 1989 was analysed.

Results A continuous improvement in relative survival rate occurred during the first year of follow-up for both colonic and rectal cancer. Some improvement was also seen during follow-up years 2–5, but this was much more pronounced during the last period (1985–1989) for rectal cancer in the county of Uppsala. The improvement was particularly marked during follow-up years 3–5.

Conclusion There are strong indications from this study that altered primary treatment for rectal cancer results in improved long-term survival.

Colorectal cancer is the fourth commonest malignant disease worldwide, with an estimated 678 000 new cases diagnosed in 1985[1] and about 394 000 deaths annually[2]. About one-third of these deaths occur from rectal cancer. In Sweden it is the third commonest form of cancer. As in other common cancers, little improvement in cure rates has occurred during the past few decades. Surgery is still the main treatment for patients with primary rectal cancer, but few studies have focused on the question as to whether the surgical technique has influenced long-term survival. As few controlled trials have been performed, comparisons between surgical techniques are based mainly on historical controls. Total mesorectal excision (TME), popularized by MacFarlane *et al.*[3], and extended lymphadenectomy, as practised by many Japanese surgeons[4], have both been claimed to improve not only local recurrence rate, but also long-term survival.

Adjuvant treatments, such as radiotherapy in rectal cancer and chemotherapy in both rectal and colonic cancer, were long considered to have no beneficial effects[5]. More recently a number of controlled trials have indicated that not only local recurrence rate in rectal cancer but also survival in colorectal cancer may be influenced by one, or a combination, of these modalities[6–17]. The survival benefits are still small, however, and their clinical relevance, particularly in combination with optimal surgery, is still under debate[18,19].

In a previous investigation overall and relative survival rates between the years 1960 and 1981 were studied on the basis of the Swedish Cancer Registry[20]. A slight improvement in relative survival was seen. The improvement was most pronounced during the first months of follow-up. Reduced postoperative mortality was considered to be the most likely major explanation for the trend towards a more favourable prognosis.

The University Hospital in Uppsala introduced preoperative radiotherapy and TME as a combined routine in 1985. At that time this was not widely performed in the rest of Sweden. In light of this the authors raised the following hypotheses. First, the relative survival rate of patients with rectal and colonic cancer would improve continuously during the first year after diagnosis over a 5-year diagnostic period to the same extent in all counties. Death during the first year is mainly a result of postoperative mortality and primarily irresectable tumours or metastatic disease found at diagnosis. Neither of these factors could be influenced by TME or preoperative short-term radiotherapy. Second, the relative survival rate of patients with rectal cancer in years 2–5 of follow-up would, in the county of Uppsala, show a particularly large improvement in the 5-year period of 1985–1989. There is no reason to expect such an improvement elsewhere. Third, no differences would be observed for colonic cancer, as those patients were not treated differently in the county of Uppsala.

The aim of the present study was to determine whether this change in primary treatment for rectal cancer has had any impact on survival in accordance with the predefined hypotheses. As patient selection may substantially influence the results, any comparisons of cohorts have to be population-based. The authors took advantage of the completeness of the Swedish Cancer Registry and compared the relative survival rate in the county of Uppsala with that in the rest of Sweden.

Patients and methods

Swedish Cancer Registry

Since 1958 all newly diagnosed cases of malignant disease have been reported to the National Cancer Registry. Repeated analyses have shown that registration is almost complete, with a deficit of less than 2 per cent[21]. The registry does not contain data on tumour stage, surgical curability or other clinical factors. Dates and causes of death are transferred annually from the Causes of Death Registry by computerized link.

Patients

The study period covered 1960 to 1989. During that period, 1736 cases of invasive carcinoma of the colon and 1060 cases of invasive carcinoma of the rectum were reported to the registry from the county of Uppsala, and 69 657 and 39 855 cases, respectively, in the rest of Sweden (*Table 1*). *Table 1* also shows

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Table 1 Number of patients with colonic or rectal cancer in the county of Uppsala and the rest of Sweden between 1960 and 1989

	County of Uppsala					Rest of Sweden				
Year of diagnosis	Total no. of patients	No. of autopsies	Metachronous cancer	Lost to follow-up	Included	Total no. of patients	No. of autopsies	Metachronous cancer	Lost to follow-up	Included
Colonic cancer										
1960–1964	188	36	0	6	146	8036	1361	11	164	6500
1965–1969	234	56	0	2	176	9792	1873	40	120	7759
1970–1974	282	90	3	0	189	11 258	2460	118	45	8635
1975–1979	302	68	2	0	232	12 329	2251	149	19	9910
1980–1984	348	40	6	0	302	13 659	1962	261	17	11 419
1985–1989	382	50	11	0	321	14 583	1691	410	8	12 474
Total	1736	340	22	8	1366	69 657	11 598	989	373	56 697
Rectal cancer										
1960–1964	126	12	1	1	112	4852	434	16	87	4315
1965–1969	142	17	0	1	124	5585	651	34	61	4839
1970–1974	185	34	3	1	147	6222	859	88	14	5261
1975–1979	167	22	7	0	138	7001	734	84	10	6173
1980–1984	209	15	5	0	189	7902	692	107	8	7105
1985–1989	231	16	3	0	212	8293	540	159	10	7584
Total	1060	116	19	3	922	39 855	3900	488	190	35 277

carcinoma diagnosed at autopsy, patients lost to follow-up, and patients with a second, metachronous cancer, all of whom were excluded from the analyses. The number lost to follow-up was very small (less than 0·5 per cent) and was mainly a result of emigration or incorrect individual identification numbers, which made it impossible to match records from different registries. The patients included were divided into six groups according to predefined 5-year periods of diagnosis. The deadline for follow-up was 30 April 1994.

Surgical technique

In the mid-1980s TME was introduced at the University Hospital in Uppsala. Separate high ligations of the inferior mesenteric vessels were performed to define the proximal limits of the lymphatic clearance. The rectum was mobilized with sharp dissection under direct vision in the avascular plane outside the fascia rectalis and Denonvillier's fascia, excising the whole mesorectum leaving the somatic structures of the autonomic nerve plexuses behind. This is in contrast to 'standard surgery', applied earlier in Uppsala, in which the mesorectal envelope was, in most patients, entered by blunt dissection.

In upper-third tumours there was no strict application of the total removal of the whole length of the mesorectum. In these patients the mesorectum was divided horizontally at least 5 cm below the tumour.

Statistical methods

Observed survival rates (OSRs) for all causes of death were calculated by the actuarial method[22]. To correct these rates of death to exclude causes other than colorectal cancer, relative survival rates (RSRs) were calculated as the ratio of the OSR to the survival rate expected during the same period in a group of people in the general population, divided according to 5-year age groups and sex[23,24]. The standard error (s.e.) of the OSRs was calculated from Greenwood's formula[25], and the s.e. of the RSRs was computed as s.e. (OSRs)/expected survival[26]. A 95 per cent confidence interval (c.i.) was calculated from point estimates and s.e. on the basis of a normality assumption.

Multivariate analyses were performed to estimate the independent effects of age, diagnostic period, sex, county (Uppsala county *versus* others), and year of follow-up. The primary aim of these analyses was to test the predefined hypotheses regarding survival in the county of Uppsala compared with all other counties. The analyses were based on grouped annual data and a generalization of the proportional hazards model in which the rectal cancer hazard rate was assumed to be additive to the hazard rate in the general population[27]. This model was formulated as a generalized linear model and estimates were obtained by the maximum likelihood method, using GLIM (Numerical Algorithms, Oxford, UK) statistical software[28]. Categorical explanatory variables were used. Stratified models and models with interaction terms were also estimated. (The authors model the excess hazard among patients with rectal cancer compared with the general population, i.e. 'the disease-specific survival with respect to rectal cancer'.) Data from the first 5 years of follow-up were used.

The estimated models were compared with respect to deviation, which describes the fit of the model. Deviation of the same order as the degrees of freedom is normally taken as an indication of a reasonable fit. The authors used the difference in deviation in combination with the pattern and size of the parameter estimates as an indicator of the quality of the different models. The results are given as relative hazard (RH) of dying from rectal cancer with 95 per cent c.i.

Results

Five-year RSRs showed that patients with cancer of the colon had a somewhat better prognosis than those with rectal cancer in all 5-year time periods except in the county of Uppsala during the period 1985–1989, when the opposite was seen (*Table 2*). Women had a generally more favourable prognosis than men (data not presented). More than 90 per cent of mortality from colorectal cancer occurred within the first 5 years (*Table 2*; these results are similar to those presented previously for the period 1960–1981[20]). The 1-, 5-, and 10-year RSRs for both rectal and colonic cancer were higher the later that the cancer was diagnosed (*Table 2*), and the improvement was most pronounced during the first year of follow-up. However, there was a particular reduction in the risk of death among patients with rectal cancer diagnosed in the county of Uppsala in 1985–1989 between 1 and 5 years after diagnosis (*Table 3*).

Survival curves comparing patients diagnosed before and after 1985 also showed an improved survival rate for patients with rectal cancer diagnosed after 1985 in the county of Uppsala that is not seen in the rest of Sweden (*Fig. 1*). No such difference was seen for cancer of the colon (data not presented). For 1985–1989, the 5-year RSRs for cancer of the rectum were 61·9 per cent (95 per cent c.i. 53·2–70·6) in the county of Uppsala and 50·9 per cent (95 per cent c.i. 49·5–52·3) in the rest of Sweden.

Table 2 Relative survival rates for patients with colonic and rectal cancer

	Follow-up in county of Uppsala (years)			Follow-up in rest of Sweden (years)		
Year of diagnosis	1	5	10	1	5	10
Colonic cancer						
1960–1964	64·9 (56·6–73·2)	49·5 (39·2–59·8)	44·8 (32·2–57·3)	63·3 (62·1–64·5)	41·5 (40·1–42·9)	39·5 (37·8–41·2)
1965–1969	68·6 (61·2–76·0)	43·3 (34·3–52·3)	41·1 (30·3–51·9)	66·7 (65·6–67·8)	45·2 (43·9–46·5)	41·8 (40·2–43·4)
1970–1974	77·1 (70·5–83·7)	63·8 (54·6–73·0)	58·9 (47·0–70·8)	67·3 (66·3–68·3)	46·0 (44·7–47·3)	42·8 (41·3–44·3)
1975–1979	72·8 (66·6–79·0)	53·7 (45·5–61·9)	43·7 (33·9–53·5)	69·4 (68·4–70·4)	48·4 (47·2–49·6)	45·5 (44·0–47·0)
1980–1984	73·7 (68·2–79·2)	59·8 (52·3–67·3)	54·3 (44·7–63·9)	73·3 (72·4–74·2)	53·1 (52·0–54·2)	50·2 (48·8–51·6)
1985–1989	78·0 (73·0–83·0)	50·3 (43·2–57·4)		75·3 (74·5–76·1)	54·6 (53·5–55·7)	
Rectal cancer						
1960–1964	66·7 (57·3–76·1)	38·6 (27·5–49·7)	28·8 (16·6–41·0)	66·3 (64·8–67·8)	36·6 (34·9–38·3)	32·6 (30·7–34·5)
1965–1969	71·8 (63·2–80·4)	38·4 (28·0–48·8)	34·0 (21·8–46·2)	69·7 (68·3–71·1)	41·5 (39·8–43·2)	36·7 (34·8–38·6)
1970–1974	76·8 (69·2–84·4)	45·3 (35·1–55·5)	46·2 (33·3–59·1)	72·1 (70·8–73·4)	43·1 (41·5–44·7)	39·2 (37·3–41·1)
1975–1979	75·1 (67·1–83·1)	52·8 (41·8–63·8)	47·0 (33·3–60·7)	75·1 (73·9–76·3)	44·2 (42·7–45·7)	39·7 (38·0–41·4)
1980–1984	74·9 (68·1–81·7)	44·1 (35·4–52·8)	36·9 (26·8–47·0)	76·4 (75·3–77·5)	48·5 (47·1–49·9)	43·4 (41·7–45·1)
1985–1989	78·4 (72·3–84·5)	61·9 (53·2–70·6)		78·6 (77·6–79·6)	50·9 (49·5–52·3)	

Table 3 Absolute and relative risks of death during different time periods after diagnosis among patients with colonic and rectal cancer

	County of Uppsala				Rest of Sweden			
Year of diagnosis	Death risk (year 0–1)	Relative death risk (year 0–1)	Death risk (years 1–5)	Relative death risk (years 1–5)	Death risk (year 0–1)	Relative death risk (year 0–1)	Death risk (years 1–5)	Relative death risk (years 1–5)
Colonic cancer								
1960–1964	35·1	1·00	23·7	1·00	36·7	1·00	34·4	1·00
1965–1969	31·4	0·89	36·9	1·56	33·3	0·91	32·2	0·93
1970–1974	22·9	0·65	17·3	0·73	32·7	0·89	31·6	0·91
1975–1979	27·2	0·77	26·2	1·11	30·6	0·83	30·3	0·88
1980–1984	26·3	0·75	18·9	0·80	26·7	0·72	27·6	0·80
1985–1989	22·0	0·63	35·5	1·50	24·7	0·67	27·5	0·80
Rectal cancer								
1960–1964	33·3	1·00	42·0	1·00	33·7	1·00	44·9	1·00
1965–1969	28·2	0·85	46·6	1·11	30·3	0·90	40·4	0·90
1970–1974	23·2	0·70	41·0	0·98	27·9	0·83	40·2	0·90
1975–1979	24·9	0·75	29·7	0·71	24·9	0·74	41·2	0·92
1980–1984	25·1	0·75	41·2	0·98	23·6	0·70	36·6	0·82
1985–1989	21·6	0·65	21·1	0·50	21·4	0·64	35·2	0·78

Values are percentages with the period 1960–1964 taken as base. Death risk years 1–5 are calculated as 100× (1 − relative survival rate (RSR) (after 5 years)/RSR (after 1 year)). Note that 'year 0–1' is the first year of follow-up, 'year 1–5' is the second, third, fourth and fifth year of follow-up (follow-up years 2–5), as 'year' refers to a point in time and 'follow-up year' is a time interval

Corresponding figures for the period of 1960–1984 were 43·8 per cent (95 per cent c.i. 39·2–48·4) and 42·8 per cent (95 per cent c.i. 42·1–43·5) respectively.

Tables 4 and *5* show the results of the multivariate modelling for rectal cancer. The authors started by assuming that the RH in the county of Uppsala (compared with the rest of the country) was unchanged over the entire period of 1960–1989. RH was 0·92 after adjustment for effects of the other variables, a reduction that was not significant (*Table 4*). Exclusion of the latest period brought RH even closer to one (RH, 0·95). An analysis based on the period of 1985–1989 showed a considerably reduced hazard for the county of Uppsala (RH, 0·79), but this was not statistically significant. A corresponding analysis restricted to follow-up years 2–5 further reduced RH to 0·61, which was significantly smaller than 1.

To study the effects further in the county of Uppsala compared with the rest of the country, the authors postulated models that included interaction effects between county and follow-up year. This allowed RH in the county of Uppsala to vary during different follow-up years (compared with the rest of Sweden). In the period 1960–1984 no tendency towards different effects was seen in this county in different follow-up years, as shown by RHs that varied rather randomly around 1 (*Table 5*). In the latest period, 1985–1989, there was no difference in RH during the first year of follow-up (RH, 1·01) between Uppsala and other counties. During the second year there was some reduction in the county of Uppsala (RH, 0·86) and during follow-up years 3–5 there was a considerable reduction (RH, 0·31, 0·52 and 0·60). Because of the small number of deaths in this county, this reduction did not reach statistical significance.

Discussion

This study provides evidence that the change in primary treatment for rectal cancer has improved the long-term survival rate in one Swedish county. However, before drawing firm conclusions about the register-based data, some issues need to be discussed. First, not all patients in the county of Uppsala had both interventions, and some patients in other counties had either one or both of them. Second, a number of other diagnostic and therapeutic measures may also have influenced the relative survival figures. Third, different registration routines might have led to changes.

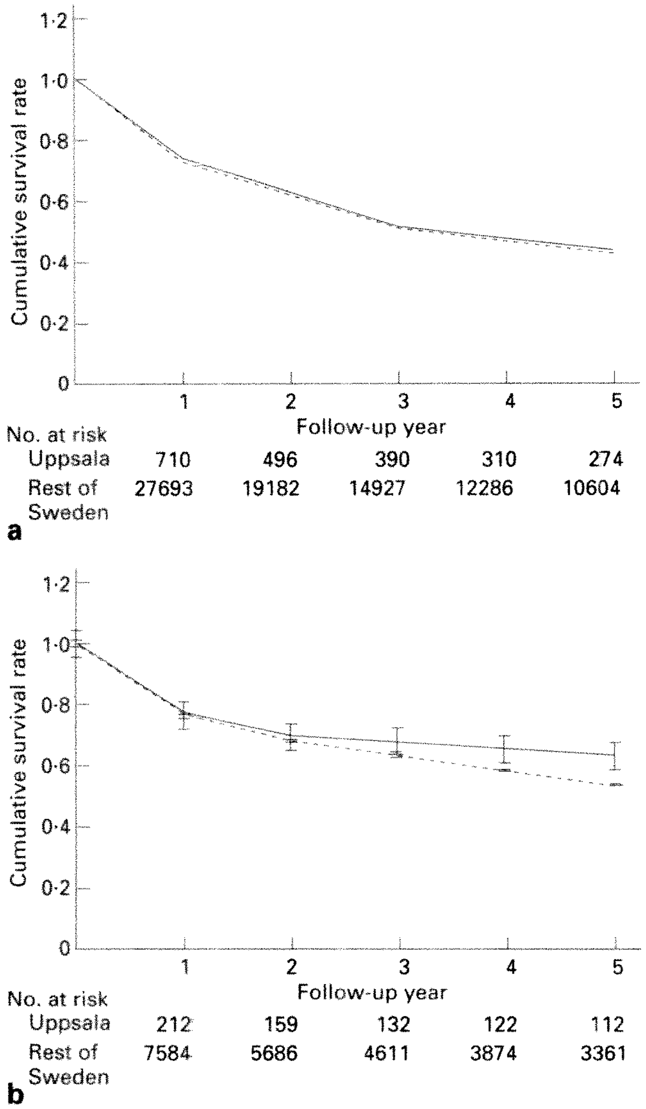

Fig. 1 Cumulative relative survival rate for patients with rectal cancer diagnosed between **a** 1960 and 1984, and **b** 1985 and 1989 for the county of Uppsala (——) and the rest of Sweden (– – – –). Bars are 95 per cent confidence intervals

Table 4 Estimates of the relative hazard of dying from rectal cancer in the county of Uppsala compared with all other counties in multivariate models containing follow-up year, sex, period, county and age

Period	Relative hazard
1960–1989	0·92 (0·82–1·04)
1960–1984	0·95 (0·83–1·08)
1985–1989	0·79 (0·59–1·07)
1985–1989 (follow-up years 2–5)	0·61 (0·40–0·95)

Values in parentheses are 95 per cent confidence intervals

Table 5 Relative disease-specific hazard in the county of Uppsala compared with all other counties, based on interaction models

	1960–1984	1985–1989
Follow-up year	Relative hazard	Relative hazard
1	0·94 (0·78–1·12)	1·01 (0·69–1·48)
Interaction terms (year of follow-up)		
2	0·96 (0·69–1·33)	0·86 (0·43–1·74)
3	1·26 (0·88–1·81)	0·31 (0·09–1·07)
4	0·80 (0·44–1·99)	0·52 (0·14–1·95)
5	1·04 (0·54–1·99)	0·60 (0·12–2·87)

Values in parentheses are 95 per cent confidence intervals

Rectal cancer surgery has always been carried out at university, district general and local hospitals in Sweden, and only occasionally by surgeons subspecializing in colorectal surgery. However, in the mid-1980s a few Swedish surgeons learned the TME technique and started to practise it. It is estimated that about 50 per cent of patients in the county of Uppsala underwent TME between 1985 and 1989. The corresponding figure in other counties may have varied between 0 and 5 per cent.

Preoperative radiotherapy using 5 × 5 Gy was first used in Uppsala in 1978[30]. Two randomized trials were initiated in Sweden in 1980, one in the Uppsala region, and one in the Stockholm–Gotland region and the city of Malmö. The Uppsala trial ceased recruitment in December 1985[31], and it was then recommended that all patients should have preoperative radiotherapy. The Stockholm–Malmö trial continued to include patients until February 1987[15], when the nationwide Swedish Rectal Cancer Trial was initiated, in which practically all Swedish hospitals participated, randomizing between surgery alone and surgery with preoperative radiotherapy[32]. According to an audit of participating hospitals, about 55 per cent of the eligible patients were included in the study (unpublished data, M. Dahlberg, L. Påhlman, B. Glimelius). It can be estimated that during 1985 and 1989, 35–45 per cent of patients with rectal cancer in the county of Uppsala had preoperative radiotherapy, whereas this figure varied between 5 and 20 per cent in the other counties.

Adjuvant chemotherapy was not used in Sweden during 1985–1989 and the effects of chemotherapy for metastatic disease on survival are limited[33,34]. There is no evidence of difference in registration patterns or earlier diagnosis over this period. Taken together, the authors do not consider that these, or any other factor, could have influenced the main conclusion, namely that the introduction of TME with preoperative radiotherapy on a more general basis in the county of Uppsala improved survival rates in patients with rectal cancer beyond 1 year after diagnosis. As TME has never been tested in a randomized trial but preoperative radiotherapy has[10,12,14–17], it can thus be claimed that at least radiotherapy is of importance, but it is the authors' belief that the improvement relates to a combination of the two interventions.

One limitation of this study is that, in spite of the very large number of observations overall, the number of patients in the group of specific interest (Uppsala patients with rectal cancer from 1985 to 1989) is rather small.

However, the results remain significant but require verification when data on larger groups of patients are available.

The authors believe that the rate of survival is improved, but cannot give an estimate of the degree of improvement. All patients within the defined populations were included in the analyses, i.e. both those who underwent the interventions and those who did not. Relative survival is also influenced beyond 1 year after diagnosis in primarily advanced cases and very old patients who cannot be treated adequately. These facts together indicate that the observed difference (11 percentage points; 5-year RSR 62 *versus* 51 per cent) is a minimum figure. It is possible that some of the survival benefit found in the Swedish Rectal Cancer Trial[12] (48–58 per cent) could have been achieved with TME alone if practised on a more general basis. In light of the difficulties experienced in performing controlled clinical trials dealing with surgical techniques this is unlikely to be proven[35]. Indirect evidence such as that provided by the present study, although confounded by the positive effect of preoperative radiotherapy, thus has to be the basis for the selection of treatment strategies.

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Short note

Local anal hypothermia with a frozen finger: a treatment for acute painful prolapsed piles

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The management of patients with acute painful prolapsed piles remains controversial. Anal dilatation and haemorrhoidectomy have a place, but the topical application of crushed ice is 'time dishonoured'[1]. This paper describes a method to produce local anal hypothermia and effect rapid symptom relief.

Materials and methods

Local anal hypothermia is achieved with a frozen finger made from a standard surgical glove; all fingers except the index finger are knotted at the base, the glove is turned inside out, filled with water, tied at the wrist and frozen. This produces a piece of ice covered by a single finger and most of the hand of the glove. After diagnosis the patient is positioned in the left lateral position and an attempt is made to reduce the piles; irrespective of the result of this the frozen finger is lubricated and inserted into the anal canal. The bulky part of the 'frozen finger' remains outside the canal and is taped in position.

Results

Fourteen patients with acute onset painful prolapsed piles have been treated with the frozen finger. When necessary pain was controlled initially with pethidine. Patient data are shown in *Table 1*. The frozen finger was inserted three to four times in each patient. Most found the initial insertion uncomfortable but within 3–4 min there was relief of pain which lasted up to 4 h. The finger remained frozen for 15–20 min. One patient required more than three doses of pethidine and ten received either no pethidine or one dose before insertion. Most pile masses decreased in size and remained reduced after two to three insertions.

Table 1 Patient data

Sex ratio (M:F)	10:4
Age (years)	35·9(9·8)
Hospital stay (days)	3·8(2·1)

Values are mean(s.d.)

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Discussion

If cooling is to be effective in anal canal disease the cold must be applied inside and around the anal canal. The topography of the perianal region makes it difficult to maintain constant contact of cold inside and around the anal canal and it is unlikely that effective cooling occurs with external application alone. Successful treatment of haemorrhoids by insertion of a 'cold stick' ('The Nine Minute Wonder') was reported in the *Arab Times* of Sunday 7 November 1982. Healing of anal fissures after use of a special dilator (Anokryo; PakuMed, Essen, Germany) cooled to − 15°C has been reported (M. K. Koudani and F. Beersick, personal communication). The technique described here uses a frozen finger, a device which is cheap and easy to make.

In painful prolapsed piles the anal canal is painful and 'tight' because the internal sphincter is contracted, there is voluntary contraction of the external sphincter and there are swollen oedematous haemorrhoids. Cold probably produces analgesia by reducing cellular metabolism and decreasing sensory nerve transmission; similarly cold relaxes the sphincters by a reduction in motor nerve and muscle function, decreasing the constriction of the prolapsed piles. Cold also reduces tissue swelling and oedema by producing local vasoconstriction.

This report demonstrates that the frozen finger reduces the pain and swelling of painful prolapsed piles. The proper place of this treatment should be established by a controlled clinical trial against standard therapies.

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Significance of local recurrence of rectal cancer as a local or disseminated disease

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Background The nature of 'local recurrence' of rectal cancer remains unclear.

Methods Fifty-nine patients with locally recurrent rectal cancer who underwent extended repeat resections including total pelvic exenteration (39) and sacrectomy (43) were reviewed. Twelve patients had distant metastases before or at the time of repeat resection.

Results The 5-year survival rate was 25 per cent. A second recurrence occurred in 45 patients including five of the eight 5-year survivors. Thirty-six of these recurrences had locoregional manifestations and 29 had distant metastases. Of 18 prognostic factors examined, the most significant determinant was the postoperative carcinoembryonic antigen doubling time (CEADT), followed by the preoperative CEADT, carcinoembryonic antigen (CEA) level and occurrence of distant metastases, in decreasing order. Late onset of first recurrence was also a favourable indicator. Thus, the growth rate of the tumour had a more profound impact on survival than the current extent of tumour progression. After operation the CEADT was reduced in patients with second recurrence ($P = 0{\cdot}05$).

Conclusion Locally recurrent rectal cancer is a manifestation of disseminated disease spreading locoregionally and often to distant organs with a low probability of long-term cure. However, survival varies widely depending on the tumour growth rate, which is biologically predetermined and is also influenced by surgery.

Recently, there has been a number of reports on the results of surgery for local recurrence of rectal cancer[1–10]. According to these studies, resection can provide good palliation and prolonged survival compared with other therapeutic modalities, with 5-year survival rates ranging from 9 to 40 per cent. However, these advantages are tempered by the high incidence of postoperative complications[3,6,9,10] and the early development of a second recurrence[3]. Such events further diminish the quality of life of the patients with double stomas, and may even shorten survival. The following questions remain unanswered: (1) whether recurrence represents localized or disseminated disease; (2) what proportion of patients are really cured by surgery; and (3) which patients benefit from surgery with prolonged survival. To answer these questions patients developing recurrence despite curative surgery must undergo a highly radical repeat resection, and they must be followed for more than 5 years using modern diagnostic procedures. Few studies seem to satisfy these criteria. The purpose of this report was to analyse data from 59 consecutive cases in an attempt to answer these questions and to gain a fresh insight into the nature of this disease.

Patients and methods

Fifty-nine consecutive patients underwent wide resection for 'local recurrence' of rectal cancer between November 1978 and December 1996. Age ranged from 39 to 77 (median 61) years; there were 32 men and 27 women. The initial resections performed for the primary rectal cancer were total pelvic exenteration in two patients, abdominoperineal excision in 36 and sphincter-saving resection in 21. Before the surgery for locoregional recurrence, five patients had undergone liver resection and two had pulmonary resection for distant metastases. At repeat resection, four had liver metastases, two had lung metastases and one had both. In two patients, the concurrent metastases occurred after resection of the first metastases.

The operative techniques employed for recurrence were similar to those described previously[3], with some modifications[11]. All operations were performed with curative intent, although at least four patients were later found to have non-curative disease. Total pelvic exenteration was performed in 39 and sacrectomy in 43 patients, 11 of whom underwent additional bony resections including inferior pelvectomy[3] in seven. Pelvic exenteration was combined with sacral resection in all but two patients. Hepatectomy was performed simultaneously in four of the patients with concurrent liver metastases. In addition to inevitable loss of the lower portion of the sciatic nerve plexus in conjunction with sacrectomy, nine patients had the remaining plexus partly removed. Another two had unilateral and one had bilateral resection of the obturator nerve. Adjuvant radiotherapy was performed in 26 patients. A further five patients received radiotherapy after the second recurrence. After operation, almost all patients received oral chemotherapy of either Tegafur (600–800 mg daily; Taiho, Tokyo, Japan) or a combination of uracil with Tegafur (400–600 mg).

The patients were regularly examined for signs of recurrence by means of serum carcinoembryonic antigen (CEA) measurements, ultrasonography of the liver, chest radiography and computed tomography as well as magnetic resonance imaging and bone scintigraphy as indicated. The survival data were analysed with regard to: (1) sex; (2) type of initial surgery; (3) location of the primary tumour; (4) lymph node status; (5) histological grade of differentiation; (6) disease-free interval; (7) interval from the initial surgery to repeat resection; (8) CEA level at repeat resection; (9) doubling time of CEA (CEADT) before repeat resection; (10) CEADT after repeat resection; (11)

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distant metastases before or at repeat resection; (12) operating time for repeat resection; (13) blood loss; (14) involvement of adjacent pelvic viscera; (15) involvement of pelvic walls; (16) extent of pelvic visceral resection; (17) resection of pelvic walls; and (18) radiotherapy before the second recurrence.

The preoperative and postoperative CEADTs were obtained for 42 and 44 patients respectively in whom CEA level was serially determined. CEADT was calculated as log 2 ÷ regression coefficient, which in turn was obtained by plotting log CEA concentration against time. If log CEA did not show a linear increase in certain periods, as was often the case, regression analysis was performed for the relatively linear interval. In six patients before operation and in three after operation in whom CEA levels did not rise with time, CEADT was set to an arbitrary value of 6000 days, which was greater than any of the observed values.

To assess the prognostic value of each variable, the patients were divided into two groups by that variable and survival rate was compared between groups in terms of hazard ratio (log rank test) and difference in 5-year survival rate (z test). The Cox regression analysis was used to select the optimal set of independent predictors. Patients were divided into those with a short survival and those with a longer survival, depending on whether death from cancer occurred within 3 years (excluding cases censored within 3 years). The distribution of each variable was then compared between these groups using the χ^2 test and Wilcoxon rank test. Associations of one variable with others were evaluated by Spearman rank correlation. Logarithmic transformation was made for all positive continuous variables showing skewed distributions to the right.

Results

Survival and second recurrence

The overall 5- and 10-year survival rates were 25 and 15 per cent respectively (*Fig. 1*). Eight patients survived 5 years but five of these developed second recurrences and three died from the disease. The patient surviving for longest has been alive without disease for 152 months since pelvic exenteration and inferior pelvectomy (patient 13). Another patient (patient 26) has been disease free for 89 months since a third resection for a lung metastasis which occurred 13 months after resection of the recurrence.

Forty-five patients have developed second recurrences, of which 16 were locoregional recurrences, nine were distant metastases, and the remaining 20 had both

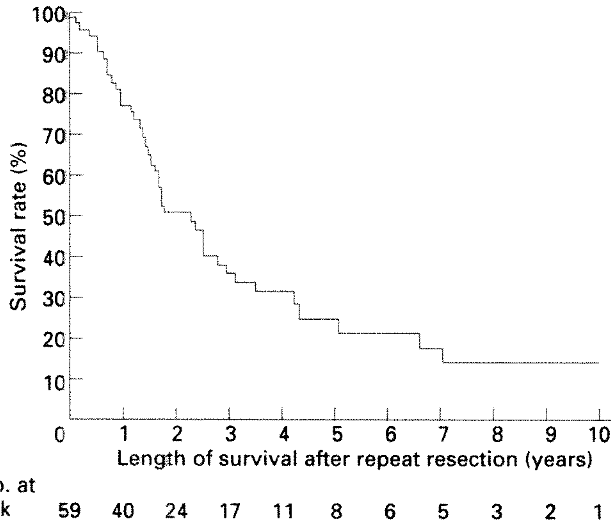

Fig. 1 Overall survival curve; 5-year survival rate, 25 (95 per cent confidence interval (c.i.) 12–38 per cent); 10-year survival rate, 15 (95 per cent c.i. 3–27) per cent; median survival time 27 months

Table 1 Statistically significant prognostic factors

Grouping by prognostic factor	No. of patients	5-year survival rate (%)	Difference in survival (%)	P†	Hazard ratio	P‡
Disease-free interval (days)						
< 1000	43	13	37	0·03	2·0	0·05
≥ 1000	11	50				
Interval from initial resection to repeat resection (days)						
< 1000	38	18	19	0·17	2·2	0·01
≥ 1000	21	38				
CEA level (ng/ml)						
> 8	25	15	26	0·006	2·5	0·02
≤ 8	26	41				
Preoperative CEA doubling time (days)						
< 100	16	0	36	0·001	4·8	0·001
≥ 100	26	36				
Postoperative CEA doubling time (days)						
< 100	24	7	58	< 0·001	9·4	< 0·001
≥ 100	19	65				
Distant metastasis at or before repeat resection						
Yes	12	0	32	< 0·001	2·8	0·02
No	47	32				
Destruction of the bony pelvis						
Yes	11	≤ 18*	≤ 10		2·4	
No	48	28				0·07

CEA, carcinoembryonic antigen. *Patient with longest survival was censored before 5 years. †z test; ‡log rank test

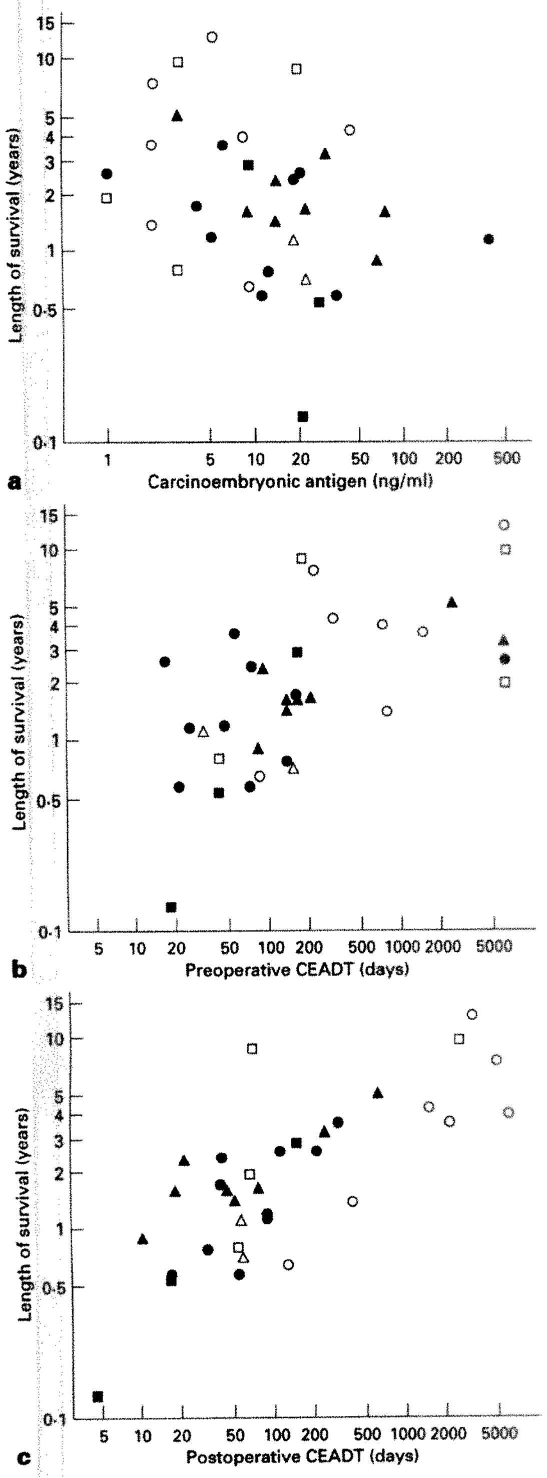

Fig. 2 Correlation of survival time with three prognostic factors. a Carcinoembryonic antigen (CEA) level ($r_s = 0{\cdot}43$ (95 per cent confidence interval (c.i.) 0·06–0·69); $t = 2{\cdot}44$, 26 d.f., $P = 0{\cdot}02$); b preoperative values of CEA doubling time (CEADT) ($r_s = 0{\cdot}53$ (95 per cent c.i. 0·19–0·75); $t = 3{\cdot}18$, 26 d.f., $P = 0{\cdot}004$); c postoperative values of CEADT ($r_s = 0{\cdot}83$ (95 per cent c.i. 0·67–0·92); $t = 7{\cdot}66$, 26 d.f., $P < 0{\cdot}001$). Data from the same 34 patients were used. ○, Living without disease; △, living with locoregional recurrence; □, living with distant recurrence; ▲, death from locoregional recurrence; ■, death from distant recurrence; ●, death from both locoregional and distant recurrence. Six patients censored within 2 years were excluded from calculations

components. The survival curve showed a rapid decline during the first 12 months. Of 13 deaths within 12 months, two were a result of postoperative complications. Of the remaining 11 deaths, two were because of locoregional recurrences alone, three a result of distant metastases, and the remaining six deaths were associated with both types of recurrence. In four patients with concurrent distant metastasis, the initial plan for staged surgery was abandoned as the disease rapidly progressed to multiple metastases. The authors consider that survival would not have been improved in these patients even if the first metastasis had been resected simultaneously.

Factors influencing outcome

If hazard ratio was used as a criterion to assess the prognostic value of each variable in survival analysis, postoperative CEADT was the most significant predictor of survival, followed by preoperative CEADT, CEA concentration and occurrence of distant metastases, in decreasing order (*Table 1*). This order remained unchanged when analyses were repeated using the same 34 patients for whom complete data on these four variables were available. A Cox stepwise analysis excluding postoperative CEADT (which was not obtainable at the time of repeat resection) showed that preoperative log CEADT was the only independent predictor ($\chi^2 = 8{\cdot}5$, 1 d.f., $P = 0{\cdot}004$).

Similar results were obtained when the distribution of each variable was compared between the shorter (less than 36 months) and longer (36 months or more) survival groups. As expected, postoperative CEADT was the strongest discriminator between the two groups despite an extremely wide range of distribution ($z = 4{\cdot}72$, $P < 0{\cdot}001$, Wilcoxon test), followed by preoperative CEADT ($z = 3{\cdot}44$, $P < 0{\cdot}001$). Compared with both CEADTs, absolute CEA level was less powerful in predicting patient survival ($z = 2{\cdot}4$, $P = 0{\cdot}02$). These three variables were again in the same prognostic order when assessed by their correlations with survival time (*Fig. 2*). As for distant metastases, ten of the 31 short-term survivors had distant metastases at or before resection, whereas only one of the 17 patients in the longer survival group had distant metastases ($\chi^2 = 4{\cdot}32$, 1 d.f., $P = 0{\cdot}04$).

In the shorter survival group, CEADT was significantly shortened after operation, indicating that tumour growth is accelerated after operation ($z = 2{\cdot}34$, $P = 0{\cdot}02$). This was also confirmed by applying the sign test to 18 pairs of data; CEADT was shortened in 14 cases after operation, compared with four patients in whom it was prolonged ($P = 0{\cdot}03$). Overall, excluding patients without second recurrence, CEADT was reduced in 19 patients whereas it was prolonged in eight ($P = 0{\cdot}05$), and the Spearman correlation between preoperative and postoperative CEADTs was 0·47 ($P = 0{\cdot}01$). There was no difference in postoperative CEADT between different types of second recurrence.

Although of lesser prognostic significance, both disease-free interval and time to repeat resection were also related to survival (*Table 1*). This is exemplified by two women who underwent repeat resection more than 100 months after the initial abdominoperineal excision. In one patient (patient 19) it took a further 96 months for the second recurrence to develop in the lung. The other woman (patient 37) has remained disease free for 49 months after combined resection of the right sciatic nerve plexus which was involved by the recurrence.

None of the other prognostic factors (not listed in *Table 1*), including the type of the initial surgery, extent of repeat resection, radiotherapy and invasion of the bladder, was significantly correlated with survival.

Discussion

Categorically, 'local recurrence' of rectal cancer has a broad aetiology. At one extreme is inadequate resection resulting in a localized residual tumour, which can be eradicated by simple repeat resection. According to Polk and Spratt[12], patients with improved survival were among those whose initial resections were performed at other hospitals and were less extensive than is usually considered adequate. Hoffman *et al.*[5] suggested that surgery after initial local excisional procedures must be placed into a separate category.

There were no such patients in this series. Despite highly radical surgery, second recurrences developed in 80 per cent of patients undergoing resection of recurrences, with a locoregional component more frequently observed than distant components. Furthermore, 21 per cent died from the disease within 1 year. Five of eight 5-year survivors developed a second recurrence. Consequently, the survival curve showed a progressive decline after 5 years, leaving only one 10-year survivor. In the series of Wanebo *et al.*[6], which included 47 patients undergoing curative sacrectomy, the 5- and 10-year survival rates were 33 and 11 per cent respectively. The survival curve indicated that one patient survived 10 years. To the authors' knowledge, there has been no other report of 10-year survival in patients undergoing such extended resection, although there are a few reports of long-term survivors after less extensive repeat resections[13]. Such long-term results appear to be worse than those after curative resection of distant metastasis to the liver or lungs.

It is generally recognized that one of the major determinants of prognosis is the extent of tumour progression, which is reflected by the size of the tumour[7,14], invasion of the pelvic wall[3,6] or adjacent viscera[14], lymph node involvement[6], distant metastases[3] and serum CEA level[6,7]. Association of poor survival with a positive surgical margin[6–9,14,15] may also be explained by tumour extension beyond the scope of resectability, although inadequate resection is another possibility. Development of metastases in remote organs has generally been regarded as the final stage of disease and the worst prognostic indicator. Of 12 patients who presented with distant metastases at or before the time of repeat resection, 11 died within 36 months. Nevertheless, the present study showed that a rapid rise of CEA concentration or decreased CEADT is closely associated with poor survival. Although postoperative CEADT was the most powerful determinant, preoperative CEADT also correlated with survival more closely than CEA level. These results could be interpreted as indicating that after curative surgery the growth rate of the tumour is a more important determinant of prognosis than the current extent of the tumour. On the other hand, the significant correlation between the preoperative and postoperative CEADTs shows that the growth rate is biologically predetermined. This interpretation is consistent with the observation[13,16,17] that the onset of recurrence is very late in some long-term survivors, although such a correlation has not been demonstrated in other reports[6,9,10].

In patients with a second recurrence, CEADT was significantly shortened after surgery, a finding consistent with occasional observations that after operation the residual tumour regains its previous size far more quickly than the preoperative growth of the same tumour. Thus, tumour growth may be accelerated by surgery, causing the early development of a second recurrence, and the extremely wide range of observed CEADT values should not be regarded merely as gross error. Initially, it was suspected that the magnitude of operative intervention was a factor influencing growth, but no significant decrease in postoperative CEADT was demonstrated after combined resection of the pelvic wall or viscera, or in groups with longer operating time or greater blood loss.

Based on these findings it is suggested that the major cause of local recurrence is cancer dissemination in surgical wounds and distant organs, rather than inadequate resection of the primary tumour, an aetiology favoured by many surgeons[18,19]. This mode of recurrence is more likely in Japan where extended surgery has been practised[20]. Although this concept is not new[21–25], there has recently been additional evidence to support it, such as port-site recurrence after laparoscopic surgery[26]. Cancer recurrence has also been described in one of the surgical incisions in the thigh where the gracilis was isolated for sphincteroplasty[27]. The clinical implications of this concept are important because, if it is valid, the incidence of recurrence could be reduced by specific prophylactic measures[28,29] including adjuvant radiotherapy and chemotherapy.

In conclusion, the majority of local recurrences of rectal cancer represent a local manifestation of a disseminated disease spreading locoregionally and often to distant organs with a low probability of long-term cure. However, survival time varies widely depending on the growth rate of the tumour, which is biologically predetermined, and also influenced by surgery. The mechanisms controlling the growth rate have yet to be elucidated.

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Effect of the introduction of total mesorectal excision for the treatment of rectal cancer

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Background Total mesorectal excision (TME) has been reported to reduce local recurrence and improve survival rates in patients with rectal carcinoma. This paper reports the problems that have arisen with the introduction of this new surgical technique.

Methods This was a prospective study of two consecutive groups of patients: one who underwent TME ($n = 76$) and one who did not (non-TME, $n = 76$).

Results Postoperative mortality rate in the non-TME and TME group was 5 and 7 per cent respectively, and the rate of anastomotic failure was 8 and 16 per cent respectively. Anastomotic leaks in TME patients were located in the mid and lower rectum. TME patients with anastomotic failure had lower anastomoses and a longer duration of operation than non-TME patients. Intraoperative problems were encountered in 71 per cent of the failures. All TME patients who had a leak required reoperation compared with 25 per cent of non-TME patients. TME patients without postoperative complications stayed significantly longer in hospital than non-TME patients.

Conclusion Anastomotic dehiscence increased after introduction of the TME technique but this improved with experience.

Rectal cancer in Norway has increased from 6·5 per 100 000 population in 1953 to 15 per 100 000 in 1992, and is expected to reach 21·5 by 2012[1]. The reported incidence of local recurrence after radical resection varies widely between 2·6 and 32 per cent[2]. In a Norwegian survey carried out between 1986 and 1988, Norstein *et al.*[3] reported a local recurrence rate of 29 per cent in patients younger than 75 years after a median observation of 60 months. Only 38 per cent of patients could have a second radical resection. Radiotherapy, before and after surgery, has been shown to reduce local recurrence, but has no effect on 5-year survival rate[4]. Postoperative irradiation in combination with chemotherapy decreases local recurrence and increases survival[5–7], and is now standard adjuvant treatment for rectal cancer stages II and III in North America.

Total mesorectal excision (TME) was introduced as a new surgical technique for rectal cancer. Local recurrence rate after 5 and 10 years is reported to be less than 5 per cent in curative cases and 5-year survival rate is 80 per cent. This is much better than any comparable studies, even with adjuvant therapy[8–10].

In 1994 the authors introduced TME for rectal cancer in Ullevaal Hospital. The aim of this report is to audit the introduction of a new surgical technique with regard to changes in various operative parameters, postoperative morbidity and mortality.

Patients and methods

Two groups of patients undergoing surgery for rectal carcinoma were prospectively compared (*Table 1*). Seventy-six consecutive patients (non-TME) had surgery between January 1992 and December 1993 before TME was introduced, using standard techniques[11]. The operations were performed by both trainees and senior surgeons.

In 1994 two senior surgeons were trained (by R.J.H.) in TME and, thereafter, participated in every subsequent operation to ensure proper technique[12]. Between January 1994 and December 1995, 76 consecutive patients underwent operation using TME. Until February 1995 a decision was made whether or not to use a diverting loop ileostomy. After that, faecal diversion became routine if the anastomosis was located below 13 cm.

In this paper the site of rectal cancer was defined according to International Guidelines for Cancer Registrars and The Cancer Registry[1] of Norway; i.e. 7 cm or less from the anal verge, low rectum; over 7 cm but less than or equal to 12 cm, mid rectum; over 12 cm but less than or equal to 20 cm, upper rectum.

All patients received antithrombotic therapy before surgery (Macrodex; Medisan AB, Uppsala, Sweden) and antibiotic prophylaxis (doxycylin 400 mg and metronidazole 1500 mg intravenously before operation).

Table 1 Clinical details

	Non-TME	TME
No. of patients	76	76
Sex ratio (men:women)	40:36	34:42
Mean (range) age (years)	69·6 (36–91)	67·9 (37–90)
Dukes stage		
A	13 (17)	18 (24)
B	30 (39)	30 (39)
C	16 (21)	12 (16)
'D'	9 (12)	8 (11)
Miscellaneous*	8 (11)	8 (11)
Abdominoperineal resection	22 (29)	28 (37)
Low anterior resection	53 (70)	44 (58)
Hartmann's operation	1 (1)	4 (5)

Values in parentheses are percentages. *Miscellaneous diagnoses included ten adenomatous lesions (three total mesorectal excision (TME), seven non-TME), four villous adenomas presumed malignant (three TME, one non-TME) and two anal carcinomas (both TME)

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Statistical analysis

Differences between the two groups were measured by contingency tables (χ^2 test). Comparisons with reference to continuous parameters were carried out using the Student's t test. Statistical significance was accepted at $P \leq 0·05$.

Results

The distance from anal verge to rectal tumour was lower in patients who had undergone abdominoperineal resection (APR) who had TME than in non-TME patients (3·1 *versus* 5·4 cm, $P = 0·004$). There was no difference in this distance in patients who had low anterior resection (LAR) (non-TME 11·6 cm; TME 11·4 cm).

The distance from the anal verge to the anastomosis in patients who had LAR was significantly less in the TME group (6 cm) than in the non-TME group (7·1 cm) ($P < 0·03$).

Operative details

TME operations were shorter than non-TME operations (mean 176 *versus* 186 min), both for APR (mean 188 min for TME *versus* 211 min for non-TME) and LAR (mean 169 min for TME *versus* 176 min for non-TME).

There were no significant differences in mean blood loss between non-TME and TME operations either after APR (1213 *versus* 1269 ml) or LAR (887 *versus* 973 ml).

Intraoperative perforation of the rectum was evident in 29 per cent of non-TME patients and 16 per cent of TME patients. Perforations were more common during APR (non-TME 59 per cent *versus* TME 32 per cent) than LAR (non-TME 13 per cent *versus* TME 7 per cent). All APR perforations were located in the anal canal and only occurred in low-placed tumours in the LAR group (non-TME 8 cm *versus* TME 3·8 cm).

Complications

There were no significant differences in the number of patients with complications (*Table 2*), or in the number of complications per patient (non-TME 2·18 *versus* TME 2·73). In-hospital mortality rates were 5 and 7 per cent in the non-TME and TME groups respectively. Anastomotic dehiscence (non-TME one; TME three) and cardiopulmonary complications (non-TME three; TME two) were the causes of postoperative death.

Table 2 Complications

	Non-TME	TME
Complications		
Total	34 (45)	40 (53)
APR	11 (50)	20 (71)
LAR	23 (43)	19 (43)
Mortality		
Total	4 (5)	5 (7)
APR	1 (5)	0
LAR	3 (6)	4 (9)
Anastomotic dehiscence	4 (8)	7 (16)
Reoperation required	1 (2)	7 (16)*
Level of anastomosis (cm)		
With anastomotic dehiscence	6·8	4·7
Without anastomotic dehiscence	7·4	5·9

Values in parentheses are percentages. TME, total mesorectal excision; APR, abdominoperineal excision of the rectum; LAR, low anterior resection. *$P = 0·05$, χ^2 test

Table 3 Number of patients with complications according to the distance of the tumour from the anal verge

	Non-TME ($n = 53$)	TME ($n = 44$)
Upper rectum	6 (30)	6 (40)
Mid rectum	12 (46)	6 (33)
Lower rectum	4 (57)	8 (73)

Values in parentheses are percentages. TME, total mesorectal excision

There were more patients who underwent APR with postoperative complications in the TME than in the non-TME group (*Table 2*). Patients with lower tumours had more postoperative complications than patients with higher tumours (*Table 3*).

All patients in the TME group with leaks underwent reoperation compared to only one in the non-TME group (*Table 2*). Mean time from operation until the leak was diagnosed was 8 (range 4–15) days in the TME group, and the mean time from first symptom of leak to reoperation was 1 day (range 6–48 h). Three of the patients with TME and a leak died.

TME patients without faecal diversion had a higher incidence of anastomotic leakage (25 per cent) than those defunctioned (8 per cent). From February 1995 faecal diversion became routine after LAR and since then there has been no leak in 31 further operations (*Fig. 1*). The anastomoses were lower in patients with leaks in the non-TME as well as in the TME group (*Table 2*). Tumours in TME patients with a leak were located either in the low ($n = 4$) or mid ($n = 3$) rectum.

Operating time in TME patients with anastomotic failure was significantly longer than in patients without (193 *versus* 164 min, $P = 0·035$) and it was also longer than in patients with other complications (193 *versus* 177 min). This could be explained by significant intraoperative problems in five of the seven patients with an anastomotic leak.

There were no correlations between anastomotic failure and ligation of the ascending left colic artery, mobilization of the splenic flexure, distribution of American Association of Anesthesiologists (ASA) scores or

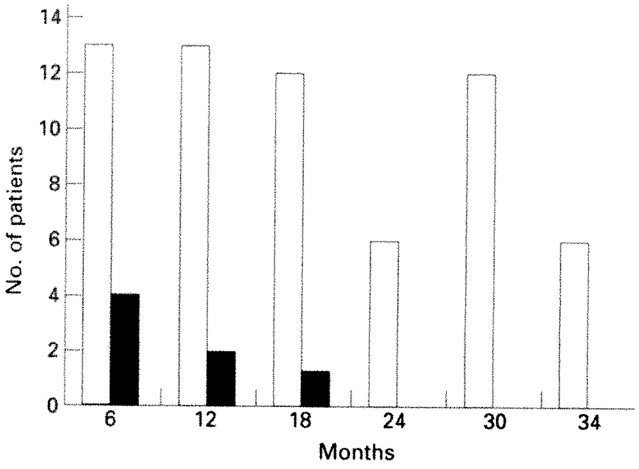

Fig. 1 Occurrence of anastomotic dehiscence in low anterior resection (LAR) with total mesorectal excision during 34 months. □, LAR; ■, leak

additional diseases (two had cardiac problems, one had cardiac problems and diabetes). The seven anastomotic failures were equally distributed among four surgeons.

Hartmann's operation

Two patients who had Hartmann's operation and TME developed complications. One patient died on the 6th day after operation from a cardiac arrest.

ASA score and complications

There was no difference in the distribution of ASA scores between non-TME and TME patients (data not shown). In the non-TME group there was an increase in complications with increasing ASA score (ASA I, 25 per cent; ASA III, 78 per cent). This was not seen in the TME group (ASA I, 54 per cent; ASA III, 59 per cent).

Postoperative stay in hospital

Patients with postoperative complications stayed significantly longer in hospital than those without (non-TME, 21·7 *versus* 9·4 days, $P<0.001$; TME, 19·2 *versus* 12·9 days, $P=0.002$). TME patients without complications stayed significantly longer in hospital than non-TME patients (TME, 12·0 days; non-TME, 9·4 days, $P<0.001$).

Discussion

In patients with primary rectal cancer the rectum and mesorectum is increasingly regarded as a single unit of regional disease to be resected *en bloc* by TME[10–13]. The introduction of a new operative technique may, however, influence postoperative morbidity and mortality.

As reported by others[14,15], postoperative complications occurred in 50 per cent of both groups. The number of complications per TME patient was higher than that per non-TME patient. This may be explained by more anastomotic failures after TME. As also reported elsewhere[16], complications were more frequent after APR than LAR in patients with low tumours. Presently, the authors perform a partial mesorectal excision for tumours above the peritoneal reflection, taking 5 cm of the rectum and mesorectum distal to the tumour.

The postoperative mortality rate was in accordance with some reports[8,14], but higher than in others[13,15]. One explanation may be that patients in this series were older. Anastomotic leakage was the most important cause of postoperative death in LAR patients who had TME[15–18]. Leaks after TME occurred between the 4th and 15th days after operation and, with one exception, all were diagnosed and operated on within 24 h of the onset of symptoms. Time to operation in those who died was even shorter (between 12 and 24 h). It seems unlikely that a routine contrast enema could have quickened diagnosis and thus reduced mortality.

The advantage of a defunctioning stoma has been reported by Karanjia *et al.*[18]. In the present study no clinically significant anastomotic leak has been seen in 31 consecutive LAR operations since faecal diversion became routine. All previous leaks occurred in patients with low anastomoses, and tumours located either in the mid or lower rectum[17].

The longer duration of operation, and observation of intraoperative incidents in five of seven TME patients who leaked, strengthens the hypothesis of a relationship between surgical problems and anastomotic dehiscence. There was no correlation between leaks and ligation of the left colic artery or mobilization of the splenic flexure[17,19].

Use of the TME technique has been reported to decrease the number of APRs[8], but the opposite was observed. The distance from tumour to anal verge was significantly less in the TME group, indicating that the reason for more APRs was the referral of a group of patients with lower tumours rather than a change in technique. A significant reduction in the distance from the anal verge to the anastomosis was observed after LAR indicating a more complete removal of the distal mesorectum by TME.

TME usually increases the duration of operation[13,14], but there was an average reduction of 10 min in this study, probably because of the participation of an experienced surgeon at every operation.

Intraoperative perforation of the rectum may spill tumour cells and increase local recurrence[20–22]. Changing operative technique to TME reduced the rate of intraoperative perforation. Most were seen during anal dissection in APR. All leaks during LAR were in patients with big tumours in the lower rectum.

Since 1996 patients with a perforation have received postoperative radiotherapy. Preoperative radiotherapy is an alternative for locally advanced tumours.

As expected, patients with postoperative complications had a significantly longer hospital stay in both groups. However, patients with LAR and TME stayed longer in hospital than patients without TME. This may be explained by the more extensive use of faecal diversion after TME and the necessary adaptation of the patients to the use of stomal bags.

On the introduction of a new surgical technique it is important to record all complications for continuous evaluation. This study has confirmed that the introduction of lower anastomoses with TME increases morbidity and mortality, though these problems can decrease with experience. The present rate of complications makes TME an acceptable risk for surgery of rectal cancer. Routine faecal diversion appears to offer protection against the complication of anastomotic dehiscence.

Acknowledgements

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Abdominal ultrasonography in the diagnosis of colonic cancer

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Background Colonic cancer is normally diagnosed by barium enema or colonoscopy. Neither investigation is ideal, especially in the elderly patient. This study investigates the potential role of abdominal ultrasonography in the diagnosis of colorectal carcinoma.

Methods Fifty-four patients with known or suspected colonic carcinoma were referred for abdominal ultrasonography. A single radiologist performed scans on these patients and the site of any colonic mass or wall thickening considered to be consistent with a colonic carcinoma was reported. All carcinomas were confirmed by histology on tissue obtained at colonoscopy or surgery against which the ultrasonographic diagnosis was compared. Colonic masses detected in patients undergoing routine abdominal ultrasonography for abdominal symptoms were also reported.

Results Forty-five of the 54 patients referred had colonic carcinoma and abdominal ultrasonography detected 43 of the tumours and correctly identified the site of 41. The sensitivity, specificity and accuracy of abdominal ultrasonography in the detection of colonic tumours considered to be consistent with a colonic carcinoma was 96, 67 and 91 per cent respectively. Seven tumours were identified in patients referred before any other investigation had been carried out.

Conclusion Abdominal ultrasonography may detect a colonic mass or wall thickening consistent with a colonic carcinoma with a high degree of accuracy and may be useful when barium enema or colonoscopy is not possible.

Colonic neoplasia is traditionally diagnosed by either barium enema or colonoscopy. Both of these investigations require unpleasant and sometimes intolerable bowel preparation, are invasive and have a recognized failure rate. In frail and elderly patients these tests cause significant distress and are often unsuccessful. Computed tomography has been reported as an alternative, less invasive investigation in such patients[1]. This paper reports experience of abdominal ultrasonography as an investigation in the detection of colonic cancer.

Patients and methods

To test the accuracy of abdominal ultrasonography in detecting colorectal carcinoma, 54 patients (25 men, 29 women) with known or suspected colorectal carcinoma were referred for abdominal ultrasonographic examination, which was performed by a single consultant radiologist with a particular interest in ultrasonography. Forty-five of the 54 patients had already been investigated by barium enema or colonoscopy and the remaining nine patients had undergone no colonic investigation before referral. The radiologist was blinded to these results and reported the site of any colonic mass or wall thickening that was considered to be consistent with a colonic carcinoma and whether liver metastases were visible. No patients with rectal tumours identified on rigid sigmoidoscopy were referred and all patients either had a colonoscopy or surgery as the 'gold standard' investigation against which the ultrasonographic diagnosis was compared.

Abdominal ultrasonography was performed using either an Aloka 650 machine with 3·5-MHz frequency probe (Keymed, Southend-on-Sea, UK) or an ATL (HDI) machine with a C 4-2 broadband width probe (Arden Press House, Letchworth, UK). A routine abdominal scan was undertaken with the addition of views of the oesophagus, stomach and the entire colon where technically feasible. Limited views of the rectum were undertaken as it was felt that this area could be viewed satisfactorily with a rigid sigmoidoscope. The features used to identify colonic cancer in this study are shown in *Figs 1–3*.

The radiologist routinely performed these additional views on all patients referred for abdominal ultrasonography for investigation of abdominal symptoms of unknown origin (usually referrals from general practitioners), and reported any colonic mass or wall thickening detected.

Results

Forty-five of 54 patients referred had colonic carcinoma confirmed histologically on samples obtained at surgery or at colonoscopy. The results of abdominal ultrasonography in detecting colonic carcinoma are shown in *Table 1*. The sensitivity of abdominal ultrasonography in detecting colonic carcinoma was 96 per cent, specificity 67 per cent and accuracy 91 per cent. The positive predictive value was 93 per cent and the negative predictive value was 75 per cent. Twelve patients with a true-positive ultrasonographic diagnosis had liver metastases identified on ultrasonography. One with a false-positive ultrasonographic diagnosis had liver metastases identified on ultrasonography; the patient was later found to have adenocarcinoma of the lung.

The site of the colonic tumour was incorrectly identified by ultrasonography in two patients (one sigmoid cancer was diagnosed as caecal and vice versa). There were two false-negative diagnoses: in one patient a locally advanced caecal cancer was diagnosed as ileocaecal tuberculosis and in another no tumour mass was identified. The stage of the tumour detected by ultrasonography in patients who had surgery was T_2 (four patients), T_3 (35) and T_4 (two).

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The tumour stage in the two patients with a false-negative ultrasonographic diagnosis was T_2 and T_3.

Barium enema missed sigmoid colon cancers in four patients because of diverticular disease and in all of these the lesion was diagnosed at ultrasonography. In one patient barium enema reported a caecal tumour as being in the sigmoid colon. In this case ultrasonography correctly identified a caecal cancer. In another patient who had a barium enema reported as normal 18 months previously, three colonic cancers were identified on abdominal ultrasonography. These were confirmed at a subsequent barium enema and then operation.

In addition, during routine abdominal ultrasonography performed for investigation of patients with abdominal symptoms of unknown origin, ten patients (five male, five female) had colonic masses identified which were considered to be consistent with colonic carcinoma. None of these patients had undergone any previous investigations and the diagnosis of colonic carcinoma was confirmed histologically in all ten patients. It is not possible to give a value for the accuracy of ultrasonography in the diagnosis of colonic carcinoma in this group of patients undergoing routine abdominal ultrasonography as the number of false-negative diagnoses is unknown. However, so far no patient who has had a

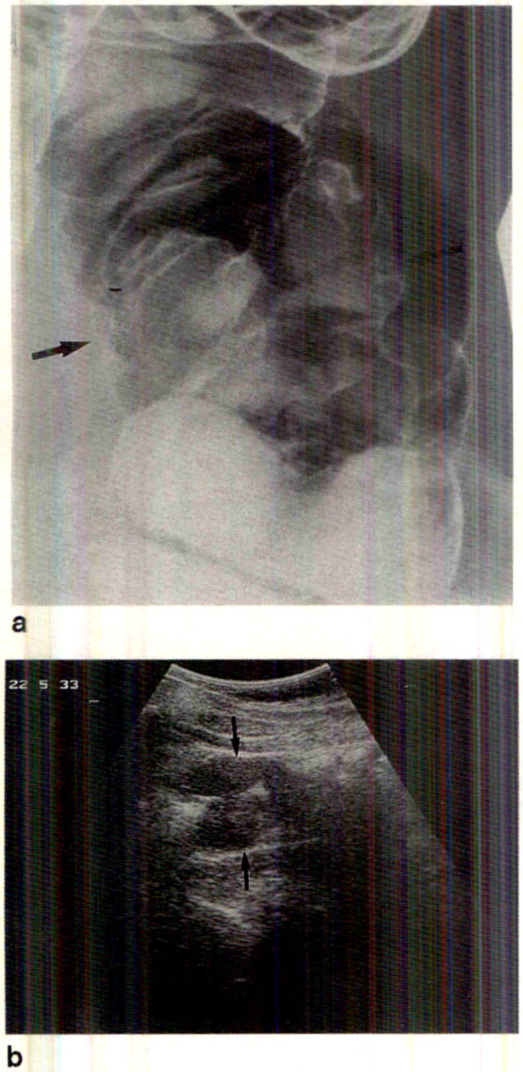

Fig. 1 A right-sided colonic tumour is shown on barium enema (**a**), and ultrasonography (**b**). The arrows delineate the extent of the tumour

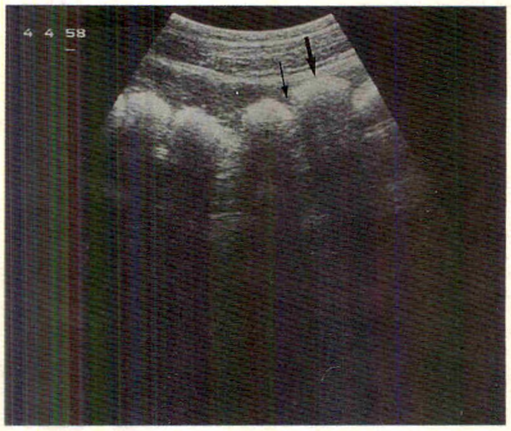

Fig. 2 Ultrasonographic appearance of a normal transverse colon in longitudinal section. The large arrow demonstrates a normal haustrum containing faeces, and the small arrow an interhaustral fold

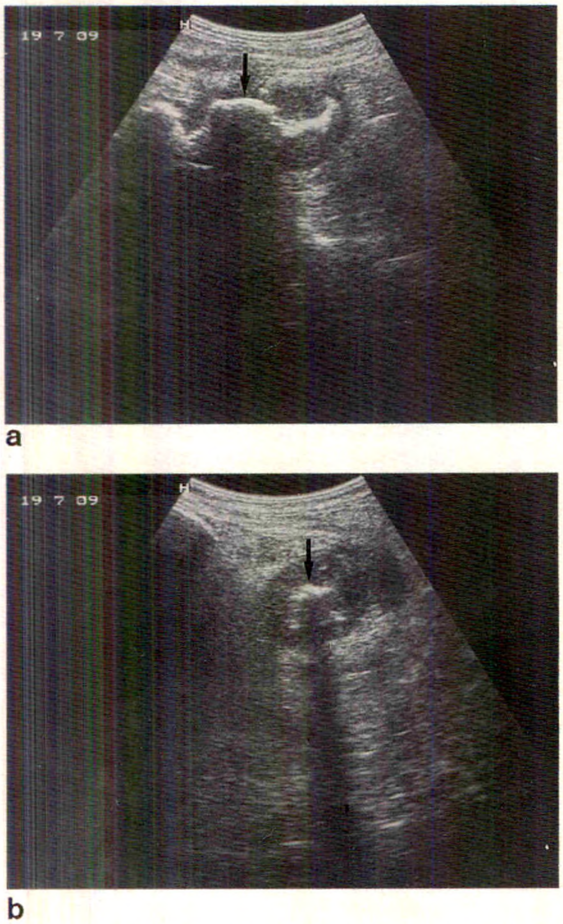

Fig. 3 Carcinoma of the transverse colon in longitudinal (**a**), and transverse (**b**) section. The arrows delineate the narrowed colonic lumen

Table 1 Results of abdominal ultrasonography in detection of colonic tumours

	Abdominal ultrasonography	
	Colonic tumour identified	No colonic tumour
Colonoscopy/surgery		
Colonic carcinoma	43	2
Normal colon	3	6

negative result on abdominal ultrasonography has subsequently been diagnosed as having a colonic carcinoma.

Discussion

Ultrasonography has been reported as being accurate in the diagnosis of several colonic conditions[2] including the site and nature of obstructing lesions[3], colitis[4], diverticulitis[5] and cancer[6,7]. Ultrasonography has been used as a screening procedure for abdominal pathology by attempting to demonstrate thickening or other modifications of the colonic wall[8] with high specificity (93 per cent), but only moderate sensitivity (77 per cent). In this study, high sensitivity and moderate specificity was achieved for identification of a colonic mass or wall thickening consistent with a colonic carcinoma. This was with a selected patient group, the majority of whom had colorectal carcinoma but these data demonstrate a much higher detection rate than was achieved in a previous study on a similar patient group where only half the tumours were detected[9]. The radiologist was unaware of the diagnosis in each patient and routinely scanned the entire colon if possible. It was also possible to detect colonic carcinomas in individuals undergoing routine abdominal ultrasonography for investigation of symptoms of unknown origin in whom there was no prior suspicion of colonic cancer.

Abdominal ultrasonography is operator dependent and the radiologist involved was experienced. Accordingly these results are likely to be at the better end of the spectrum if variability between observers is considered. However, colonic views on ultrasonography are usually ignored and this technique could easily be taught to less experienced radiologists interested in ultrasonography to allow more general use with an acceptable level of accuracy. Operator experience is also applicable to the performance and interpretation of a barium enema or colonoscopy and performance of both improves with practice.

The ultrasonographic visualization of liver metastases is likely to increase the expectation of the operator of detecting a colonic tumour but as these are identified on the same examination, they act as a stimulus to search the colon more extensively. Ten patients had colonic tumours identified on routine abdominal ultrasonography for abdominal symptoms, confirming that this technique can detect colonic tumours in a less highly selected group of patients, although it is not possible to report sensitivity and specificity for this group. As regards tumour stage, the degree of resolution was enough to detect T_2 tumours without the need to use additional intraluminal fluid which has been used in previous reports[10,11].

Abdominal ultrasonography can detect colorectal carcinoma with acceptable accuracy but what, if any, should be its role as a diagnostic modality? Barium enema and colonoscopy are the usual methods of diagnosing colorectal cancer. The resolution provided by both is good and colonoscopy allows direct visualization and biopsy of any lesion identified. Both these investigations require bowel preparation which, especially in the frail elderly patient, may produce fluid and electrolyte imbalance and are often unpleasant and may even be intolerable. Barium enema may fail if the patient has insufficient sphincter control to retain the barium and can miss lesions, particularly in the sigmoid colon when associated with diverticular disease. Failure to detect lesions can occur in up to 15 per cent of cases, most commonly due to a failure in reporting rather than failure to demonstrate the lesion[12]. Total colonoscopy may be technically impossible even in the best hands and is only achieved reliably in 70 per cent of patients in all units[13]. Both investigations can result in bowel perforation, at a rate of one in 25 000 in the case of barium enema and one in 1700 in the case of colonoscopy[14]. Computed tomography has been suggested as an alternative investigation[15], but this is time consuming, expensive and exposes the patient to significant radiation. Recent work has been published[13] on 'virtual colonoscopy' which has the potential to image the colon non-invasively and with a high degree of accuracy, but this is currently experimental and availability is likely to be limited.

At present, the experience of ultrasonographic detection of colonic tumours is encouraging but it is not enough to replace barium enema or colonoscopy routinely. However, in cases where barium cannot be retained and it is impossible to pass the colonoscope round to the caecum, such as in elderly patients, the priority is to determine whether or not there is a carcinoma present in the bowel, and this may be achieved accurately with ultrasonography.

Conclusions

Abdominal ultrasonography can detect colorectal carcinoma with a high degree of accuracy. Ultrasonography is non-invasive and well tolerated by all patients and may have a role in diagnosing colorectal cancer, especially in frail or elderly patients.

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Influence of blood components and faeces on the *in vitro* cancericidal activity of povidone–iodine

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Background Tumoricidal agents have been used to kill viable exfoliated tumour cells following colorectal cancer surgery. Recent *in vivo* experiments have thrown some doubt on the tumoricidal activity of povidone–iodine.

Methods The cytotoxic effect of distilled water and of povidone–iodine at 0·04, 0·4, 0·8, 2 and 4 per cent final concentrations on human SW620 colonic cancer cells in the presence of red blood cells, purified haemoglobin and red blood cell (RBC) membranes, plasma, albumin, faeces and bacteria was investigated. Cell viability was assessed using the trypan blue assay and MTT test.

Results The presence of albumin and plasma decreased the tumoricidal activity of povidone–iodine except for the highest concentration tested. Bacterial suspension did not influence the efficacy of povidone–iodine. Faecal material was found to have an intrinsic tumoricidal effect. Both intact and lysed RBCs very strongly inhibited the tumoricidal activity of all povidone–iodine concentrations tested. This inhibitory effect was due to haemoglobin, but not to RBC membranes.

Conclusions Low concentrations of povidone–iodine fail to kill all 'exfoliated' cancer cells in the presence of proteins, intact or lysed RBCs. Therefore, washing out of these organic materials before application of a relatively high povidone–iodine concentration (e.g. 5 per cent or greater) may be more useful in killing viable exfoliated tumour cells during surgery for colorectal cancer.

Three potential mechanisms have been proposed to explain local recurrence after 'curative' colorectal cancer surgery: incomplete primary tumour resection, metachronous carcinogenesis and implantation of viable exfoliated malignant cells[1]. The presence of viable free tumour cells in the intestinal lumen of patients with colorectal cancer, as well as the ability of these cells to proliferate and grow, have been documented[2–4]. Several tumoricidal agents have been used to eradicate these exfoliated cancer cells[5–9]. In non-randomized series of patients with colorectal cancer in whom intraoperative cytotoxic lavage of the resection margins was performed, low local recurrence rates have been observed[10–13]. Although the cancericidal ability of the antiseptic agent polyvinyl pyrrolidone–iodine (povidone–iodine) has been demonstrated *in vitro*[6,14], recent *in vivo* experiments have shed some doubt on the tumoricidal efficacy of this agent[15]. The presence of blood was found to inhibit the killing action of 1 per cent povidone–iodine on free tumour cells *in vitro*. It was suggested that several other 'organic materials' such as dietary residue, bacteria, mucus and proteins shed into the lumen might interfere eventually with the cancericidal effect of povidone–iodine.

In this study an investigation was made of the influence of bacteria, faecal material, albumin and blood components (intact and lysed red blood cells (RBCs), haemoglobin, RBC membranes and plasma) on the ability of various concentrations of povidone–iodine to kill human colonic cancer cells *in vitro*. These experiments have to be considered in the context of investigations on intraoperative preresectional orthograde whole-colon lavage using povidone–iodine to eliminate exfoliated tumour cells in patients with colorectal cancer.

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Material and methods

Tumour cell suspension

SW620 human colonic carcinoma cells were grown in monolayer culture in 75-cm^2 flasks. The medium was minimum essential medium (MEM; Gibco, Life Technologies, Merelbeke, Belgium) supplemented with antibiotics (penicillin 200 units/ml, vancomycin 100 μg/ml, streptomycin 200 μg/ml, gentamicin 50 μg/ml, Amphotericin B 2·5 μg/ml), 10 per cent fetal calf serum and the following additives: L-glutamine 2 mmol/l, insulin 20 munits/ml and dexamethasone 50 mmol/l. SW620 cells are highly tumorigenic in immune-deficient mice[16,17]. After trypsinization with a 1 in 10 solution of trypsin ethylenediamine tetra-acetic acid (EDTA) in phosphate-buffered saline (PBS) (0·5 g trypsin, 0·02 g EDTA disodium salt dihydrate and 8·5 g sodium chloride per litre), cells were pelleted and resuspended in 10 ml MEM. Cell viability was assessed using the trypan blue exclusion test. The cell concentration was adjusted to about 10^6 cells per ml of tumour cell suspension.

Tumoricidal agents

The cytotoxic effects of the following agents were studied: distilled water, povidone–iodine (Belgana, Brussels, Belgium) 0·1, 1, 2, 5 and 10 per cent in distilled water. Some 4 ml of cytotoxic agent solution were added to 2 ml of tumour cell suspension and 4 ml of 'organic material' or its solvent (in parallel control tests). Thus, the final concentrations of povidone–iodine in these experiments were 0·04, 0·4, 0·8, 2 and 4 per cent, except for testing the effect of albumin (see below).

Assessment of tumour cell viability

Cell viability was assessed using the trypan blue exclusion test. The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay was used as a supplementary biochemical test to evaluate cell viability. Each mixture of tumour cell suspension, cytotoxic agent and 'organic material' or MEM (as a control) was centrifuged and resuspended in 1 ml of MEM after removing the supernatant. Samples (100 μl) of this resuspension were placed in each well of a multi-well plate and treated as described previously[9,18,19]. Multi-well plates were then placed in a scanning spectrophotometer (enzyme-linked immunosorbent assay reader) with a filter that absorbs wavelength 595 nm maximally. High readings correspond to high intensity of dye colour and thus to a high number of viable cells able to metabolize MTT salt. As the colour of the cytotoxic agent solutions, as well as the presence of dead cells or 'organic material', may influence the result, control (blank) tests were performed simultaneously. The cells in 2 ml tumour cell suspension samples, containing 10^6 cells, were 'killed' in the presence of 8 ml acetic acid 0·01 mol/l for 30 min. After centrifugation (150 *g* at 4°C for 6 min), the pellet was resuspended in 2 ml of medium and identical quantities of cytotoxic agent solutions and 'organic material' were added. After incubation for 30 min these mixtures were centrifuged and the pellet was resuspended in 1 ml of MEM. The MTT assay was then performed as described above. The absorbance observed for these control samples was subtracted from the readings obtained for test samples. When the difference was negative, it was considered to be zero.

Organic material

Bovine serum ablumin. For the study, 2·1 g bovine serum albumin (BSA) was dissolved in 24 ml cytotoxic agent solution. To 8 ml of this mixture 2 ml tumour cell suspension were added (7 per cent BSA final concentration) and incubated at 37°C for 30 min. After centrifugation at 150 *g*, 4°C for 6 min, the supernatant was discarded and the cell pellet resuspended in 1 ml MEM to assess cell viability. Parallel control tests were performed without BSA. All experiments were performed in triplicate.

Faeces. Some 21 g of faeces were obtained from a healthy volunteer, homogenized and mixed with 84 ml freshly prepared anaerobic reducing buffer (ARB; 0·1 mol/l sodium phosphate buffer, 0·01 per cent sodium ascorbate, 0·1 per cent sodium thioglycolate). Equal amounts of faecal slurry and cytotoxic agent were preincubated overnight at 4°C. After centrifugation, 8 ml of the supernatant (4 ml faecal slurry and 4 ml cytotoxic agent) were added to 2 ml of tumour cell suspension and incubated at 37°C for 30 min. After centrifugation the cell pellet was washed three times with MEM and resuspended in 1 ml MEM. In two parallel control series, ARB or physiological saline was used without faecal homogenate to assess the eventual interference of ARB with the tumoricidal effect of povidone–iodine.

Bacteria. Colonic bacteria consisted of *Bacteroides fragilis* 10^4 colony forming units (c.f.u.) per ml, *Escherichia coli* 10^3 c.f.u. per ml, *Clostridium perfringens* and *Eubacterium* 10^5 c.f.u. per ml, and *Enterococci* 10^2 c.f.u. per ml. These bacteria were grown in Bacto Fluid Thioglycollate Medium (Difco Laboratories, Detroit, Michigan, USA) with a final pH of 7·1 at 25°C. The mixture was stored at 4°C and placed at room temperature 24 h before an experiment. In the test series, a mixture of 2 ml tumour cell suspension, 4 ml cytotoxic agent and 4 ml bacterial suspension was incubated for 30 min at 37°C. Incubation was stopped by centrifugation (150 *g* at 4°C for 6 min) and the cell pellet was resuspended in 1 ml MEM. In two parallel control series, thyoglycolate medium or physiological saline was used without bacteria to assess the eventual interference of thyoglycolate medium with the tumoricidal effect of povidone–iodine. All experiments were performed in triplicate.

Blood. The effects of intact and lysed RBCs, RBC membranes, haemoglobin and plasma (fresh frozen plasma) were studied. Fresh packed cells (not older than 5 days) were used: 56 ml of packed cells were mixed with 28 ml of physiological saline. In the test series, mixtures of 2 ml tumour cell suspension, 4 ml cytotoxic agent and 4 ml packed cells were incubated for 30 min at 37°C, followed by centrifugation (150 *g* at 4°C). The cell pellet was resuspended in 10 ml of RBC lysing buffer (RBCLB; Sigma, Bornem, Belgium; 0·83 per cent ammonium chloride in 0·01 mol/l Tris buffer) for 1 min and centrifuged (50 *g*, 4°C for 6 min). These steps were repeated five times to wash out the RBC membranes. Finally, the remaining tumour cell pellet was resuspended in 1 ml MEM and assessed for cell viability. In a pilot study (three tests), RBCLB was shown not to affect tumour cell integrity as assessed by the trypan blue exclusion test. All experiments were performed in triplicate.

Haemoglobin and RBC membranes were prepared as follows. The same amounts of packed cells and physiological saline as used for the study of intact RBCs were lysed by freezing at − 80°C (overnight) and thawing at 42°C for 1 h. This freeze–thawing procedure was repeated and complete RBC lysis was confirmed microscopically. Lysed RBCs were centrifuged at 20 000 *g*, 4°C for 30 min, to spin down the membranes. This procedure was repeated up to five times until the supernatant was colourless. All supernatant was collected (and stored at 4°C) and freeze-dried for 24 h. The resulting haemoglobin powder was resuspended in 84 ml PBS and the haemoglobin content was shown to be similar to the original value before freezing. The pellet containing the RBC membranes was washed with physiological saline and centrifuged (20 000 *g* at 4°C for 6 min). After five washings, the membranes were resuspended in 84 ml of MEM. In the test series 2 ml of tumour cell suspension were mixed with 4 ml of cytotoxic agent and 4 ml of either membrane or haemoglobin suspension. Again, control series were performed in parallel experiments using 4 ml of MEM or 4 ml of PBS instead of the membrane or haemoglobin suspensions. All experiments were performed in triplicate.

Plasma. Some 12 ml of fresh frozen plasma were preincubated with 12 ml of each cytotoxic agent under study. To 8 ml of this mixture 2 ml of tumour cell suspension were added and incubated at 37°C for 30 min. After centrifugation at 150 *g*, 4°C for 6 min, the supernatant was discarded and the cell pellet was resuspended in 1 ml MEM to assess cell viability. Parallel control tests were performed using physiological saline instead of plasma. All experiments were performed in triplicate.

Statistical analysis

The data are presented as mean(s.d.). The Wilcoxon signed rank test was used for paired comparisons. Spearman's rank correlation was used to assess the relationship between variables determined by two different methods. $P < 0·05$ (two tailed) was considered significant.

Results

Effect of bovine serum albumin

Seven per cent BSA did not affect tumour cell viability. The partial tumoricidal effects of distilled water or povidone–iodine 0·08 per cent (final concentration) were found to be increased in the presence of 7 per cent BSA: 64(4·7) per cent viable tumour cells in BSA-free distilled water *versus* 42(2·2) per cent in distilled water with BSA ($P < 0·05$), and 63(7·5) per cent in povidone–iodine 0·08 per cent *versus* 37·5(5·8) per cent in povidone–iodine 0·08 per cent with BSA ($P < 0·05$). In contrast, the presence of 7 per cent BSA decreased the tumoricidal activity of povidone–iodine for other concentrations tested; 27·6, 19·2 and 13·5 per cent of cells remained viable in the presence of 7 per cent BSA *versus* 1·8, 0 and 0 per cent in BSA-free povidone–iodine 0·8, 1·6 and 4 per cent respectively. Povidone–iodine at an 8 per cent final concentration could still kill all tumour cells.

Cell viability as assessed by trypan blue exclusion and MTT tests showed comparable results ($r_S = 0·91$).

Effect of bacteria

The presence of bacteria minimally affected tumour cell viability in the absence of cytotoxic agent. The presence of bacteria did not significantly influence the efficacy of distilled water or povidone–iodine in several concentrations, except for the lowest concentration tested, although the thyoglycolate medium protected tumour cells slightly against the action of povidone–iodine. Povidone–iodine at greater than 2 per cent concentration had a 100 per cent killing rate, either in the presence or absence of bacteria during incubation. The results obtained using the trypan blue method to assess the cell viability were similar to those with the MTT test ($r_S = 0{\cdot}94$).

Effect of faecal slurry

Faecal material, but not its solvent ARB, affected tumour cell viability significantly in the absence of cytotoxic agent. Faecal slurry significantly increased the tumour cell killing rate of distilled water or lower concentrations of povidone–iodine, although ARB is shown to protect tumour cells. The killing rates as determined by two methods were similar ($r_S = 0{\cdot}79$).

Effect of blood components

Both intact and lysed RBCs strongly inhibited the tumoricidal activity of povidone–iodine of all concentrations tested. At povidone–iodine 2 per cent final concentration, about 12 per cent of tumour cells remained viable. Povidone–iodine 4 per cent could not be tested because of the occurrence of precipitation. Again, observations made with both methods for assessing cell viability were similar ($r_S = 0{\cdot}87$).

To determine whether this inhibitory effect of RBCs was due to haemoglobin or to the RBC membranes, the experiments were repeated with the purified fractions. RBC membrane had no effect. In contrast, haemoglobin completely blocked the tumoricidal action of povidone–iodine, including the 2 per cent final concentration (*Fig. 1*). Povidone–iodine 4 per cent could not be tested because of precipitation.

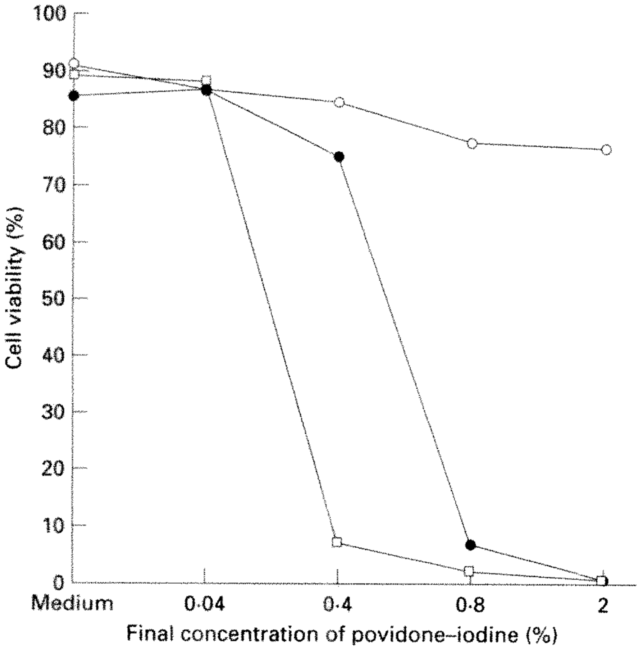

Fig. 1 Effect of haemoglobin (○), phosphate-buffered saline (●) and 0·9 per cent sodium chloride (□) on the tumoricidal activity of povidone–iodine as determined by trypan blue assay. Values are the mean of three tests

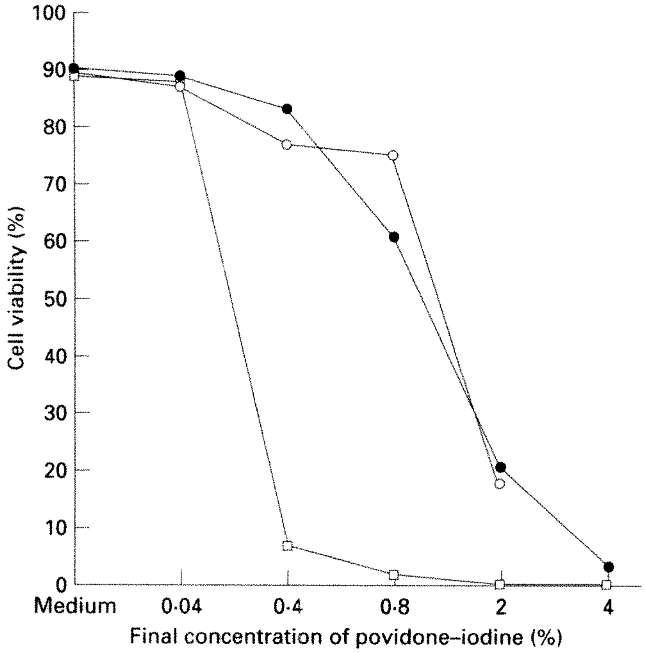

Fig. 2 Effect of intact red blood cells (○), plasma (●) and 0·9 per cent sodium chloride (□) on the tumoricidal activity of povidone–iodine as determined by trypan blue assay. Values are the mean of three tests

Plasma also inhibited the tumoricidal activity to the same extent as RBCs (*Fig. 2*). Both methods of assessing cell viability showed high correlation ($r_S = 0{\cdot}96$).

Discussion

Povidone–iodine is often used to irrigate the distal rectum or to perform on-table lavage preparation of the colon in order to allow a single-stage resection for colorectal cancer and anastomosis in the unprepared colon[20]. An antiseptic agent, it had also been shown to have tumoricidal activity on isolated or exfoliated viable tumour cells[6]. Recently, however, the suggestion was made that the tumoricidal efficacy of povidone–iodine may be blocked by the presence of organic material[15]. Normal stool contains about 80 g of soluble proteins per kg, but additional proteins may be secreted or released by colorectal cancer[21]. Also, significant amounts of blood might be present in the neighbourhood of the resection margins at the anastomosis or in the operative field.

Albumin is the most abundant serum protein present in stool of patients with colorectal cancer[22]. In the present experiments, albumin and serum proteins were shown to inhibit the tumoricidal activity of povidone–iodine as determined by two methods to assess cell viability. This inhibitory effect of proteins is thought to be due to the binding of iodine from povidone–iodine. High concentrations of povidone–iodine were able to saturate the binding sites of proteins, while retaining sufficient iodine to achieve a high killing rate.

Bacterial suspension was found not to interfere with povidone–iodine activity but was observed to have a moderate intrinsic tumoricidal activity. In contrast with bacteria, faecal material was shown to have a much higher degree of tumoricidal activity. Stool is known to contain considerable proteolytic activity that may arise from endogenous or microbial proteases[21]. This illustrates and explains the hostile character of the colonic content to exfoliated tumour cells.

Others have observed that blood affects the tumoricidal activity of povidone–iodine[15] or proflavine hemisulphate[23]. The present results indicate that lysed as well as intact RBCs inhibit remarkably the tumoricidal activity of povidone–iodine. In addition, free haemoglobin is the responsible component for the major inactivation of povidone–iodine by RBCs. In a pilot study, the authors found that povidone–iodine 2 per cent and 5 per cent can induce RBC lysis by as much as 3 and 12 per cent respectively, after incubation for 24 h.

In conclusion, povidone–iodine at a concentration of 2 per cent or more was confirmed to kill the selected tumour cells *in vitro*. However, organic materials, such as proteins (albumin at a concentration of 7 per cent or more, plasma), RBCs and, especially, free haemoglobin, were found to inhibit the tumoricidal activity of povidone–iodine. As the free iodine level is dependent on the concentration of the solution, dilute solutions of povidone–iodine have a smaller iodine reservoir and therefore less killing capacity. Consequently, removal of organic material might be beneficial in surgical practice, together with the use of a higher concentration of povidone–iodine (5 per cent or more) to achieve killing of all exfoliated tumour cells.

Acknowledgements

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Histamine in human breast cancer

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Background Histamine inhibits lymphocyte function *in vitro* at concentrations of greater than 10^{-6} mol/l. The aim of this study was to determine whether histamine concentrations in breast cancers were sufficient to produce an immunological effect.

Methods Tumour and adjacent normal breast content of histamine was measured using a radioenzymatic assay in 29 patients having surgery for breast cancer.

Results The median content of histamine in breast cancer tissue was 5·4 (range 0·9–27·3) μg/g (median concentration $4{\cdot}5 \times 10^{-5}$ mol/l), and was significantly greater than that in adjacent breast tissue ($P = 0{\cdot}007$).

Conclusion The concentration of histamine in breast cancer was sufficient to inhibit lymphocyte function and could be locally immunosuppressive.

There is evidence to suggest that histamine plays a significant role in cancer. Functional histamine receptors have been demonstrated in some tumour cell lines[1,2]. Histamine has also been implicated as a mediator of proliferation in breast cancer through its binding to novel intracellular receptors that are closely associated with antioestrogen binding sites[3]. Mast cells have been reported in high numbers around the periphery of various solid tumours and are known to be of prognostic value in colorectal cancer[4,5]. Specific inhibitors of the histamine synthesizing enzyme, histidine decarboxylase, have been shown to inhibit tumour growth in different animal models[6], and *in vitro*[7], suggesting that *de novo* synthesized histamine stimulates tumour growth. Other groups have found that histidine decarboxylase activity reflects the tumour mitotic index and is increased in human breast and colorectal cancer[8].

While histamine in physiological concentrations is an immunostimulant, it is thought to be immunosuppressive at high concentrations[9]. Histamine inhibits lymphocyte function[10,11] and has been reported to stimulate lymphocyte migration inhibitory factor at a minimum concentration of 10^{-6} mol/l[12,13]. A 40 per cent inhibition of phytohaemagglutinin-induced lymphoblastic response *in vitro* was achieved with a histamine concentration of 5×10^{-6} mol/l, and reversed by cimetidine[14]. Patients with colorectal cancer who were treated with a short course of cimetidine at the time of tumour resection had a 34 per cent trend to survival advantage at 3-year follow-up. Two other groups have recently reported on the survival of patients with colorectal cancer treated after operation with cimetidine[16,17]. Although there are important differences between these studies, all appear to show similar survival advantages[18]. A survival advantage has been demonstrated with cimetidine treatment in gastric cancer[19]. No clinical trials in breast cancer have been reported.

A significant increase of tumour infiltrating lymphocytes (TILs) was seen in patients with rectal cancer treated with cimetidine. Although histamine content in tumour tissue has been studied in animal models, few have examined the histamine content of human tumours. It is not clear whether the effect of cimetidine on TILs is related to histamine in tumours.

The aim of this study was to establish whether sufficient histamine was present in human breast cancers to affect lymphocyte activity.

Patients and methods

Specimens were taken from patients who formed part of a double-blind randomized clinical trial of adjuvant cimetidine treatment for breast cancer. This trial had been approved by the South Sydney Area Health Service ethics committee and informed consent was obtained from patients before treatment and investigations.

Tissue specimen preparation

Fresh tissue specimens, comprising tumour and adjacent healthy tissue, were chilled immediately on ice. Tumour tissue was always taken from the leading edge of the tumour. Specimens were chopped, weighed (average weight 300 mg), deproteinized in 2 ml of cold perchloric acid 0·1 mol/l and stored at −70°C until needed. On thawing, specimens were centrifuged at 3600 *g* for 15 min at 10°C and the supernatant was further diluted with water to minimize enzyme inhibition. The person performing the assay was blinded as to whether a specimen was tumour or adjacent tissue.

Histamine assay

The methods employed were those described by Henry *et al.*[20]. Each sample was assayed in triplicate, with and without a histamine standard. The concentration of histamine in the original specimen was expressed as micrograms of histamine per gram of fresh tissue weight. [^{3}H] *S*-adenosyl methionine and histamine-*N*-methyltransferase were purchased from Du Pont (Sydney, Australia).

Preliminary experiments were aimed at spiking various samples with known quantities of histamine to determine histamine retrieval, and to ensure the accuracy of the technique.

Histology

Routine pathology reports were used to access tumour histological type and differentiation. Staining for mast cells was carried out on 4-μm sections of formalin-fixed paraffin-embedded tissue from the tumour margin of 25 patients, using toluidine blue stain for mast cells, with which mast cell granules

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stain deep purple. A positive control of skin tissue with pronounced mast cell infiltration was included in the staining run. For each tumour ten high-power (magnification × 400) fields were examined and mast cells counted; the mean number for the best six fields was then compared with tumour histamine content.

Statistical analysis

Individual specimens were analysed in parallel (tumour *versus* healthy tissue) with Student's t test. Collated specimens were analysed with the Wilcoxon test for non-parametric data.

Results

Twenty-nine patients with a mean(s.d.) age 60 (13) (range 31–83) years were studied. The majority of tumours were invasive ductal carcinomas ($n = 22$), one of which was a high-grade recurrent tumour. The remainder included invasive lobular ($n = 3$), cribriform ($n = 1$), mucinous ($n = 1$) and mixed ductal–lobular carcinomas ($n = 2$). One patient with invasive ductal cancer had Paget's disease of the nipple. Tumours were graded histologically according to the methods described by Bloom and Richardson[21].

Six of the 29 tumour specimens had no healthy breast tissue for comparison as insufficient tissue was available. Median(s.e.) histamine content in tumour tissue (5·4(1·3) μg/g) was significantly higher than in adjacent breast (1·3(0·4) μg/g) ($P = 0·007$, Wilcoxon test). Similarly, median histamine concentration was higher in tumour tissue (mean $4·9 \times 10^{-5}$ *versus* $1·2 \times 10^{-5}$ mol/l) (*Fig. 1*).

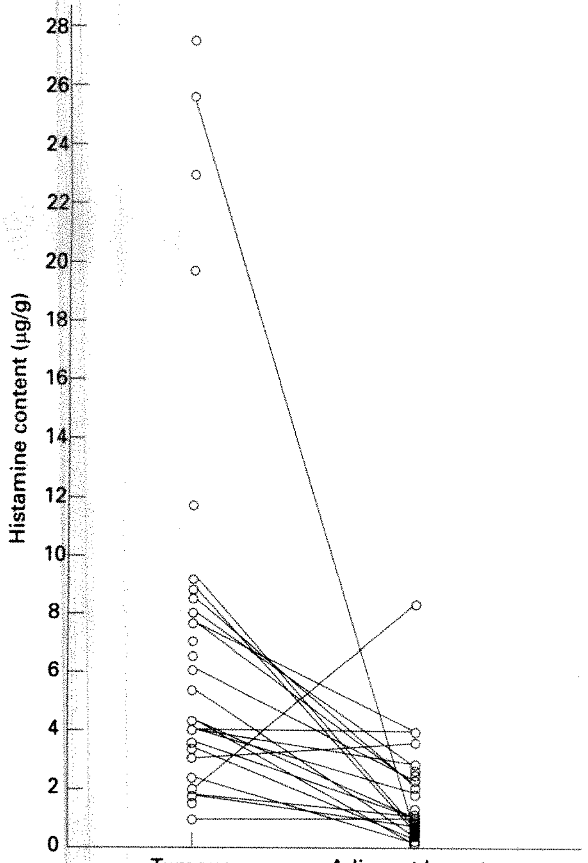

Fig. 1 Mean histamine content in breast cancer specimens: tumour tissue histamine ($n = 29$) compared with adjacent tissue ($n = 23$) from the same patient

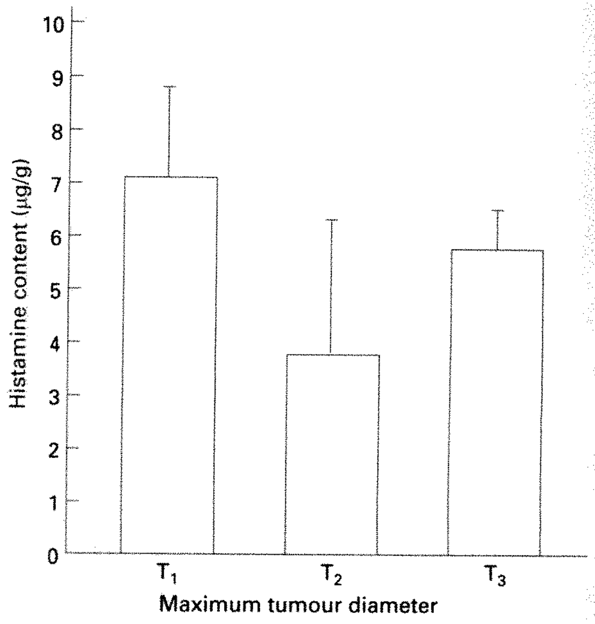

Fig. 2 Tumour tissue histamine content *versus* tumour size. Tumours were categorized according to maximum tumour diameter by the tumour node metastasis (TNM) classification: T_1, 2 cm or less ($n = 12$); T_2, more than 2 and less than 5 cm ($n = 13$); T_3, greater than 5 cm ($n = 4$). Values are median(s.e.). No significant correlation was found

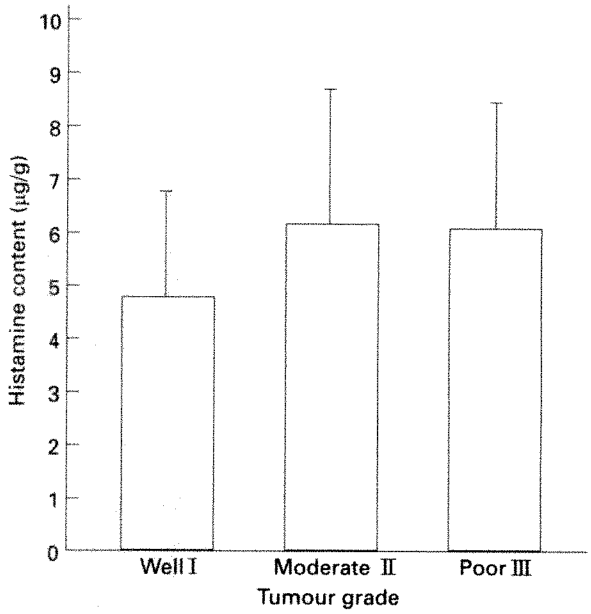

Fig. 3 Tumour tissue histamine content *versus* tumour histological grade. Histological grade was determined according to methods described by Bloom and Richardson[21]: grade I, low grade; grade III, high grade. Values are median(s.e.). Grade I, $n = 3$; grade II, $n = 13$; grade III, $n = 10$

Some 19 of 23 breast tissue specimens demonstrated a tumour tissue histamine content significantly greater ($P < 0·05$, Student's t test) than that of adjacent healthy breast tissue; only three had a tumour tissue histamine content lower than that of adjacent breast. All the tumour specimens had a histamine concentration greater than 1×10^{-6} mol/l. There was no difference in median(s.e.)

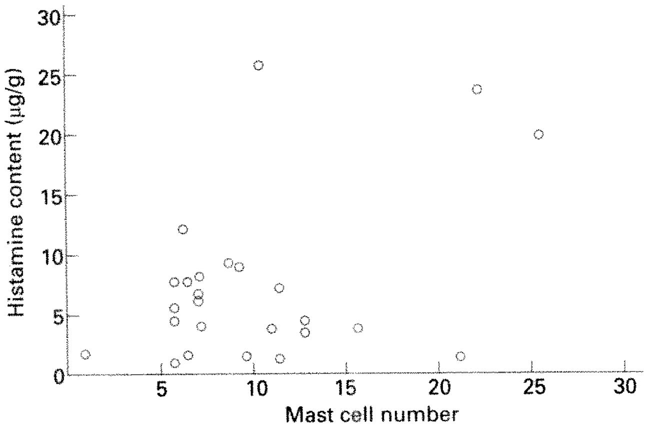

Fig. 4 Relationship between tumour histamine content and mast cell numbers (mean of six best fields) in breast cancer

histamine concentration between controls and patients taking cimetidine (6·5(4·4) *versus* 6·3(8·1) μg/g respectively). There was no correlation between tumour histamine content and tumour size (*Fig. 2*), grade (*Fig. 3*) or differentiation (data not shown). Similarly, there was no relationship between mast cell number (mean of six best fields) and histamine concentration ($n = 25$ tumours) (*Fig. 4*).

Discussion

This study demonstrates a significant difference between the histamine content of human breast cancers and of adjacent breast tissue. Cimetidine treatment did not affect tumour tissue histamine concentration, although it may increase the proportion of tumours with a prominent number of TILs. Similarly, Chanda and Ganguly[22] found median(s.e.) histamine content to be higher in breast tumour tissue (82·06(12·02) μg/g) than in adjacent healthy tissue (32·55(2·97) μg/g). These levels are considerably higher than those reported here, but the sample size was small ($n = 4$). García-Caballero *et al.*[3,28] found median(s.e.) histamine content to be lower in breast tumour tissue (4·05(27·0 μg/g) than in healthy tissue (6·10(0·46) μg/g), despite reporting a higher histidine decarboxylase activity in the tumour tissue. The range of histamine concentrations in the present study is in agreement with levels reported by García-Caballero *et al.*, although histamine content was significantly higher in breast tumour than in healthy tissue. It is possible that García-Caballero and co-workers found lower concentrations of histamine in tumour tissue because samples were taken from the centre of the mass[23]. It has been reported that histamine concentration is highest in the peripheral layer of actively growing tumour[24].

The high histamine concentration in breast tumours supports the hypothesis that histamine has an immunosuppressive effect. The correlation between histamine content and TILs, or the effect of cimetidine treatment and survival, is not yet known. Histamine content did not correlate with tumour size, grade or differentiation, which suggests that any relationship between histamine and tumour growth is complex. Tumour histamine levels in animal models can reflect the size of the tumour[6] suggesting that small, newly diagnosed tumours could synthesize more histamine than larger advanced tumours. The cellularity of tumour samples in this study would have been considerably higher than that of the surrounding breast tissue, which may explain the higher histamine concentrations present.

Histamine has an established immunosuppressive effect on lymphocyte proliferation at concentrations greater than 1×10^{-6} mol/l[10,12,13,25]. Khan *et al.*[26] also found that histamine concentrations between 10^{-8} and 10^{-4} mol/l suppressed the generation of class I-specific cytotoxic T lymphocytes. The effects of histamine on other parameters of lymphocyte function, such as migration, have not been fully established. Similarly, the effect of histamine on the various subsets of lymphocytes is not known. The relationship between histamine levels and TILs is likely to be complex, rendering its prognostic value controversial. Several groups have reported that a high density of lymphoreticular cells correlates with a favourable prognosis[27–30], whereas others have found no correlation at all[31,32]. In invasive ductal breast cancer, however, there is a positive correlation between the density of lymphoreticular cells and survival[27,28]. Lymphocytes infiltrating breast cancer have been shown to have a low level of natural killer cell activity[33], which might relate directly or indirectly to tumour histamine concentration.

The role of mast cells in breast cancer is also poorly defined. The mast cell stabilizing compound FPL 55618 inhibits rat mammary adenocarcinoma 13762NF by up to 70 per cent[34]. One report on mast cell density around breast tumour tissue concluded that high mast cell density (greater than 10 per mm^2 of stroma) correlated with improved survival; however, the survival curve from which the conclusions were drawn appeared to show the converse[35]. Some of the histamine measured in the breast tumours in the present study may have been released from mast cells at the time of tumour resection, although there was no correlation between mast cell number and histamine content in this study. There is good evidence to suggest that mast cell histamine plays a prominent role in tumour growth, but the source of the histamine has yet to be determined.

In conclusion, there are sufficiently high levels of histamine in breast cancers to inhibit lymphocyte activity.

Acknowledgements

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Long-term beneficial effects of a gastric reservoir on weight control after total gastrectomy: a study of potential mechanisms

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Background Weight loss after total gastrectomy is a regular occurrence. Reconstruction with a gastric substitute has been suggested to facilitate recovery, but few randomized studies are available.

Methods In a randomized study comparing subtotal, total and total gastrectomy with an S-shaped pouch, 36 patients who had total gastrectomy with or without a pouch survived for more than 3 (mean 5·2) years. Body composition (four-chamber model, dual-energy X-ray absorptiometry, anthropometric data) was evaluated before operation, after 12 months and at long-term follow-up. Food intake was registered as a 4-day food record at 12 months and at long-term follow-up.

Results At long-term follow-up those allocated to the gastric substitute arm had lesser degrees of weight loss consisting mainly of the depletion of body fat stores, whereas lean body mass showed no significant decrease when adjusted for the process of ageing. There was no significant difference in food intake.

Conclusion Reconstruction with an S-shaped gastric substitute facilitates long-term recovery after total gastrectomy and should be considered when the prognosis is favourable.

Weight loss is a regular consequence of radical surgery for gastric cancer, irrespective of whether total or subtotal gastrectomy is performed[1–3]. Data have now been collected from controlled clinical trials to allow characterization of the effects of similar operations on nutritional intake as well as on body compartments during the first postoperative year[4]. The weight loss occurs during the first 3 months[1,3], whereafter weight stabilizes. Patients with a subtotal gastrectomy seem to consume somewhat fewer calories during the same period, after which their intake improves[3]. The construction of a gastric reservoir after total gastrectomy or leaving a gastric remnant after subtotal resection seems, however, not to improve the nutritional intake within the first 12 months after gastrectomy. Similarly, the mechanisms involved in weight development have been assessed by determining changes in body composition by use of total body potassium (TBK) content and total body water (TBW) calculations and thereafter estimating body cell mass (BCM), extracellular water (ECW), fat-free extracellular solids (FFESs) and body fat (BF). BCM seems to remain essentially unchanged over this limited time period in contrast to the BF compartment which decreases by 40 per cent during the first 6 months[4]. Concomitant with that, a significant decrease in triceps skinfold (TSF) thickness occurs, whereas only marginal changes in arm muscle circumference (AMC) and hand grip strength are observed[4,5]. These observations contrast, however, with reports in which the outcome of different gastric substitution techniques was assessed during somewhat different surgical clinical trial designs[5–8]. One important factor that has to be considered is that significant benefits of a certain reconstruction might not appear until a considerable time has elapsed after the actual operation.

Therefore, in the present study the long-term consequences of total gastrectomy on nutritional intake and body composition were determined with particular emphasis on the eventual beneficial effect of having a gastric substitute.

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Patients and methods

A patient population was recruited into a controlled randomized clinical trial. Patients with distal carcinoma were randomized to subtotal or total gastrectomy with a simple Roux-en-Y oesophagojejunostomy, and those with more proximally located carcinoma to total gastrectomy with or without an S-shaped gastric substitute[3]. Details of the randomization are illustrated in *Fig. 1*. Data are now presented for the 36 patients who had total gastrectomy and a minimal follow-up of 3 (mean 5·2) years.

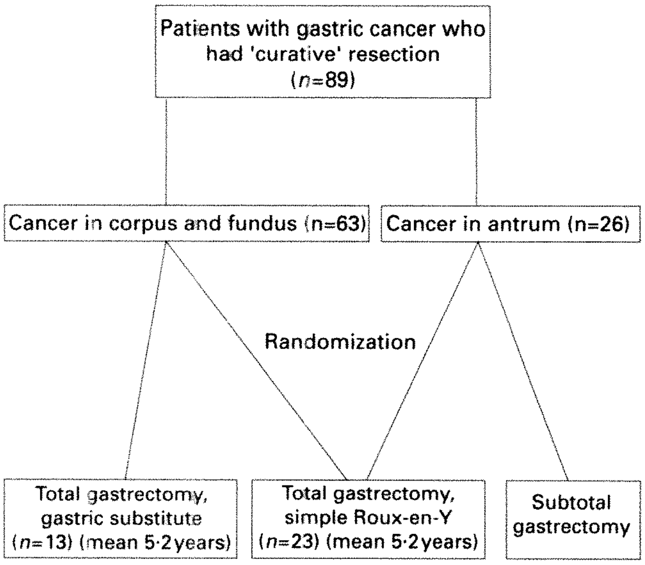
Patients with gastric cancer who had 'curative' resection (*n*=89)
Cancer in corpus and fundus (n=63)
Cancer in antrum (n=26)
Randomization
Total gastrectomy, gastric substitute (*n*=13) (mean 5·2 years)
Total gastrectomy, simple Roux-en-Y (*n*=23) (mean 5·2 years)
Subtotal gastrectomy

Fig. 1 Algorithm demonstrating the randomization and distribution of the originally enrolled patients. The 36 patients still alive after more than 3 years constitute the study population

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During that time interval, 24 of the originally enrolled patients died from recurrent cancer, nine succumbed from other causes unrelated to the gastric carcinoma and six died during the first postoperative 6 months as described in detail previously[9]. Two additional patients were lost to follow-up because they refused to participate in any postoperative investigation. The operative procedures and preoperative and peroperative assessments have been reported in detail elsewhere[3,9].

Body composition was determined before operation, after 12 months and at the time of long-term follow-up by assessment of TBK content and TBW. TBK was determined by counting the 1·46-MeV γ radiation from the naturally present isotope ^{40}K, giving a standard deviation of approximately 80 mmol[10]. TBW was determined by isotope dilution of tritiated water. The coefficient of variation of a single TBW determination was 3·2 per cent[10]. In the four-compartment model used, body-weight (BW) is the sum of the four compartments: BCM, ECW, FFECSs and BF[10]. In this model the input variables are TBK, TBW, BW and normal body-weight (BW_{norm}). BCM is calculated where BCM (kg) = TBK (mmol) × 0·00833. Intracellular water is assumed to be 75 per cent of BCM; thus ECW = TBW − 0·75 × BCM. FFECSs are assumed as a constant fraction (12 per cent) of BW_{norm}. The BW_{norm} for each patient was taken from an adult control population[10]. BF is derived from the difference: BF = BW − (FFECSs + BCM + ECW). TSF thickness was measured with a Harpender caliper and AMC was calculated. Hand grip strength was measured before operation, after 12 months and at the end of the study. At follow-up, dual-energy X-ray absorptiometry (DEXA) (LUNAR DPX-L; Luna-Radiation Corporation, Madison, Wisconsin, USA) was also used to measure body composition[11].

Nutritional intake

Food intake was assessed and adjusted as reported previously[3], and a 4-day record was completed after 12 months and at the time of long-term follow-up. Food records were converted from household measures to gram weights and nutrient values by the use of national food consumption tables[12,13]. The weight of the main mean consumed each day was converted to decilitres (100 ml) to assess portion volume[3].

To validate further the recording of oral intake, faecal nitrogen losses (N_F) were measured together with urinary excretion of urea (N_U) over 3 days[14]. In all, information on these variables was acquired for 59 patients during the first 12 months. Dermal losses (N_D) were estimated to be 1 g/day[10,15]. Consequently, total protein losses were calculated from the formula $6{\cdot}25 \times (N_F + N_U + N_D)$ and then related to the reported protein intake at the different study points.

To compensate for changes in postoperative weight, food intake was also related to preoperative weight. This consideration was taken to circumvent the pitfall of having an undernourished but weight-stable postoperative patient reporting a false accurate food intake if calculated per kilogram of actual BW.

Statistical analysis and ethics

Analysis of the data was by the χ^2 test, regression analysis and Student's t test when applicable. $P < 0{\cdot}05$ was considered significant.

The study protocol was approved by the local ethics committee, and informed consent was obtained from each patient.

Results

The preoperative and peroperative characteristics of the patients and the histopathological features are detailed in *Tables 1* and *2*. At endoscopy, carried out at 12 months after operation and at the time of long-term follow-up, no oesophagitis or fibrous stricture of the distal oesophagus or oesophagojejunal area was observed. As reported previously[3], weight loss occurred early after gastrectomy and a weight of 10 per cent below the preoperative state remained at 1 year after operation (*Table 3*). When a paired analysis was carried out, total weight loss amounted to 10 kg compared with 1 kg ($P < 0{\cdot}01$) for patients having the Roux-en-Y and gastric substitute respectively, with the according percentage difference (*Fig. 2a*). From 12 months after operation and to the end of follow-up, patients with a substitute had gained 1 kg whereas those having a simple Roux-en-Y procedure had lost an additional 4 kg. However, when weight development was studied specifically in the time period from 3 to 10 years after operation, a cumulative increase in weight was observed in both groups of gastrectomized patients (*Fig. 3*).

Table 1 Demographic data in patients allocated to Roux-en-Y reconstruction or gastric substitute after total gastrectomy

	Roux-en-Y (n = 23)	Gastric substitute (n = 13)	Total (n = 36)
Mean age at operation (years)	63	64	63
Mean (range) follow-up (years)	—	—	5·6 (3–10)
Sex ratio (M:F)	15:8	9:4	24:12
Mean preoperative weight (kg)	69·5	67·0	68·7
Non-smoking	11	7	18
Alcohol abuse	2	1	3
Coexisting disease			
Cardiac			
Angina pectoris	3	1	4
Previous myocardial infarction	1	0	1
Hypertension	6	2	8
Pulmonary			
Obstructive	0	1	1
Chronic bronchitis	3	1	4
Other	1	1	2
Other			
Diabetes mellitus	0	1	1
Miscellaneous	3	1	4
Previous history of malignancy	2	2	4

Table 2 Tumour status and histopathological features in patients with gastric carcinoma treated by total or subtotal gastrectomy

	Roux-en-Y (n = 23)	Gastric substitute (n = 13)	Total (n = 36)
Tumour type			
Adenocarcinoma			
Diffuse	16	5	21
Intestinal	5	1	6
Mixed	1	3	4
Linitis plastica	0	1	1
Lymphoma or sarcoma	1	3	4
Depth of growth			
T_1	4	4	8
T_2	14	8	22
T_3	5	1	6
Nodal status			
N_0	15	9	24
N_1	5	4	9
N_2	3	0	3

Table 3 Body composition (four-compartment model) as assessed before operation, and 12 months and 5 years after gastrectomy with or without a gastric substitute

	Total gastrectomy	Gastric substitute	Total
Weight (kg)			
Preop.	67·6(2·7) (23)	67·1(3·3) (11)	67·4(2·1) (34)
12 months	63·0(3·4)† (15)	64·2(3·0) (12)	63·6(2·4) (27)
5 years	57·9(3·1)† (22)	64·6(3·4) (11)	60·0(2·4) (33)
Body fat (kg)			
Preop.	15·2(1·6) (16)	12·8(2·1) (8)	14·4(1·3) (24)
12 months	10·5(1·8)† (13)	9·8(1·7) (12)	10·2(1·2)† (25)
5 years	8·7(1·5)† (22)	10·7(1·5) (11)	9·4(1·1)* (33)
Total body potassium (mmol)			
Preop.	3064(185) (16)	3138(261) (8)	3088(148) (24)
12 months	3024(160) (13)	3142(192) (12)	3081(122) (25)
5 years	2843(174)* (22)	3096(211) (11)	2927(136)† (33)
Extracellular : intracellular water			
Preop.	1·0(0·1) (16)	1·0(0·1) (8)	1·0(0·0) (24)
12 months	1·1(0·0) (13)	1·0(0·1) (12)	1·0(0·0) (25)
5 years	1·1(0·1)* (22)	1·0(0·1) (11)	1·1(0·1) (33)
Triceps skinfold thickness (mm)			
Preop.	14·1(1·1) (18)	13·2(2·6) (9)	13·8(1·3) (27)
12 months	10·4(1·0)† (21)	11·3(1·1) (9)	10·7(0·8)* (30)
5 years	9·3(0·9)† (17)	11·8(1·7) (7)	10·0(0·8)* (24)
Arm muscle circumference			
Preop.	24·7(0·7) (18)	24·4(0·9) (9)	24·7(0·5) (27)
12 months	23·3(0·6)* (23)	24·6(1·0) (9)	23·7(0·5)* (32)
5 years	23·9(0·8)* (17)	23·1(1·6) (7)	23·7(0·7) (24)

Values are mean(s.e.m.) with number of patients in parentheses. *P < 0·05, †P < 0·01 *versus* preoperative value (paired t test)

Table 4 Food intake and portion sizes 12 months and 5 years after total gastrectomy with or without a gastric substitute, and energy losses at the corresponding follow-up occasions

	Total gastrectomy	Gastric substitute	Total
Energy intake (kJ)			
12 months	9490(720) (18)	8146(511) (11)	8983(494) (29)
5 years	9155(607) (20)	8389(753) (10)	8904(473) (30)
Protein intake (g)			
12 months	83(6·2) (18)	76(4·7) (11)	80(4·3) (29)
5 years	81(6·2) (20)	70(6·2) (10)	77(5·1) (30)
Carbohydrate intake (g)			
12 months	273(25·8) (18)	206(13·5) (11)	247(17·7) (29)
5 years	263(16·9) (20)	233(19·9) (10)	253(13·2) (30)
Fat intake (g)			
12 months	96(9·6) (18)	90(7·8) (11)	94(6·6) (29)
5 years	87(7·5) (20)	86(9·1) (10)	87(5·8) (30)
Energy intake in relation to weight			
5 years (kJ/kg)	149·4(7·1) (19)	135·6(13·8) (9)	144·8(6·7) (28)
Energy intake in relation to preoperative weight			
5 years (kJ/kg)	135·6(6·2) (20)	138·1(8·8) (9)	136·0(5·4) (29)
Daily faecal energy loss			
5 years (kJ)	1523(209·7) (16)	1008(126·4) (7)	1414(153·6) (23)
Maximal portion size (dl)			
12 months	7·3(0·6) (17)	7·3(0·4) (8)	7·3(0·4) (25)
5 years	7·5(0·5) (19)	8·1(0·8) (8)	7·7(0·4) (27)
Mean portion size (dl)			
12 months	5·9(0·5) (17)	6·0(0·4) (8)	5·9(0·3) (25)
5 years	5·9(0·4) (19)	6·5(0·5) (8)	6·1(0·3) (27)

Values are mean(s.e.m.) with number of patients in parentheses

Total energy intake at 1 year after gastrectomy was 8980 kJ and thereafter did not change with time (*Table 4*). It was not found that patients under-reported markedly, according to the cut-off score developed by Goldberg *et al.*[16]. There was no tendency towards larger food intake among those having a gastric substitute when this was related to the preoperative weight, but a trend existed towards larger maximal and mean portion sizes. When daily faecal energy losses were assessed years after gastrectomy, no significant difference was observed

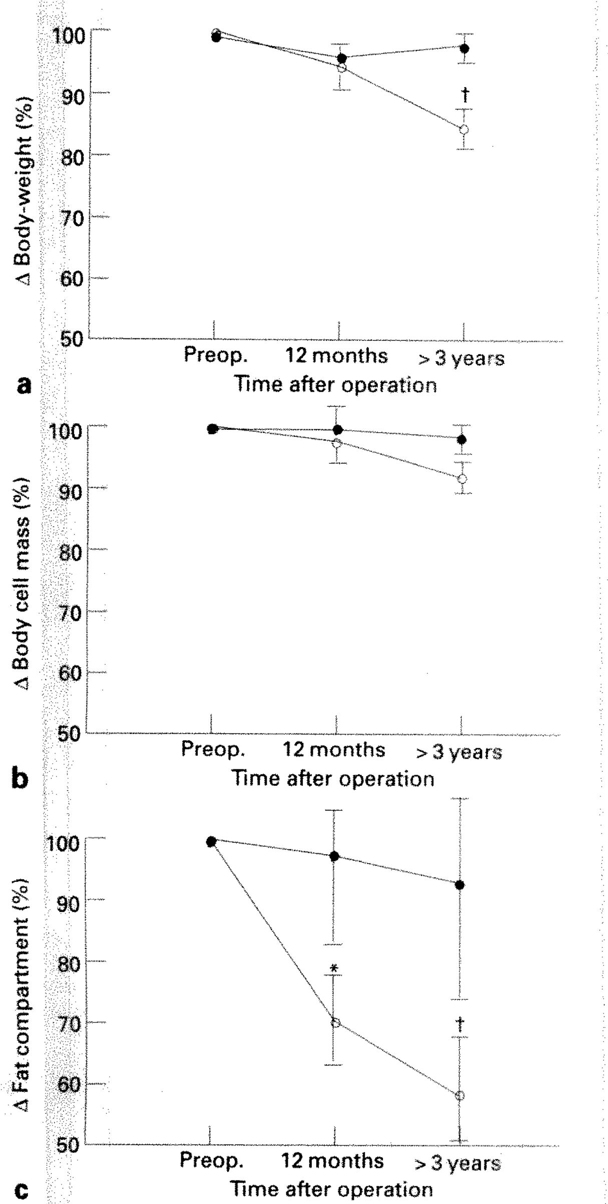

Fig. 2 Mean(s.e.m.) percentage changes of **a** body-weight and of (**b** and **c**) different body compartments compared with the preoperative state at 12 months and at long-term follow-up (mean 5·2 years). In **b** changes in body cell mass are given and in **c** changes in the fat compartment. ○, Patients with a simple Roux-en-Y reconstruction; ●, those with a gastric substitute. $^*P < 0{\cdot}05$, $^{\dagger}P < 0{\cdot}01$ (Roux-en-Y *versus* gastric substitute, Student's *t* test)

between the two study groups, but again numerically smaller losses were recorded in those having a gastric substitute (*Table 4*). When energy requirement was estimated based on basal metabolic rate curves[3,17], food intake in patients with a gastric reservoir slightly exceeded the calculated needs (42 kJ/day). Those with a simple Roux-en-Y oesophagojejunostomy had a calculated deficit of 419 kJ/day.

Protein intake was studied also in relation to the estimated losses. Higher protein intake was observed than the calculated losses, with a positive balance amounting to 6·5 g.

Parallel use of the DEXA scan and the four-compartment model to determine body compartments

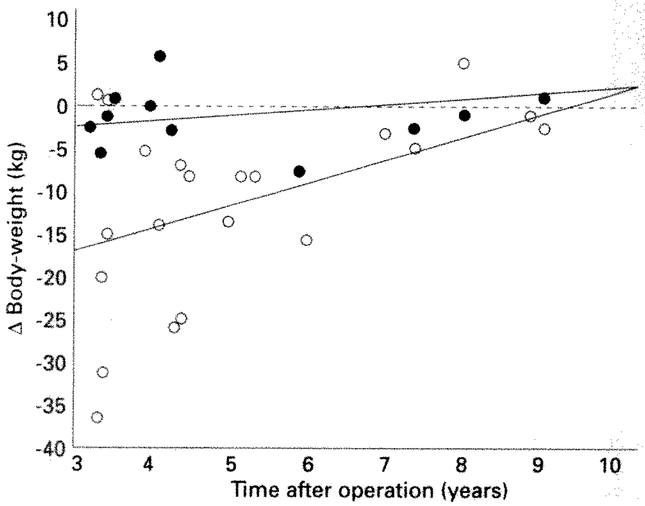

Fig. 3 Weight loss after operation in gastrectomized patients with or without a gastric substitute when assessed 3–10 years after operation. ○, Patients with a simple Roux-en-Y reconstruction; ●, those with a gastric substitute

revealed an excellent correlation with respect to both lean body mass ($r^2 = 0{\cdot}95$) and BF compartment ($r^2 = 0{\cdot}82$).

BCM, as assessed by TBK content, decreased significantly from preoperative values when re-estimated more than 3 years after gastrectomy ($P < 0{\cdot}0002$) (*Table 3*). However, when corrections were made for ageing and the associated natural decrease in lean body mass[10], this decrease in BCM from the preoperative value was not statistically significant (*Fig. 2b*). The fat compartment of the body decreased during postoperative follow-up ($P = 0{\cdot}01$) (*Fig. 2c*), a difference that became even more apparent when adjustment was made for the process of ageing. These observations were also corroborated by the recordings of TSF thickness, which decreased significantly from the preoperative value ($P = 0{\cdot}03$), but again AMC remained essentially unchanged over time. In parallel with the weight change, from 1 year after operation onwards, patients having a gastric substitute had an increase in TSF thickness of 1·2 mm, compared with an additional loss of 1·0 mm in those having a simple Roux-en-Y reconstruction when a paired analysis was carried out.

Discussion

One important factor behind the lack of consensus over the short- and long-term consequences of total gastrectomy and the impact of different reconstructive procedures is that very few controlled, clinical, randomized studies have been conducted and reported. Another explanatory factor might be that the period of observation after gastrectomy is of particular importance where the beneficial effects of, for instance, a gastric substitute become apparent only after a considerable period of time. This is illustrated by the present series in which a cumulative weight gain was observed many years after operation. In recent years some important observations have been published from trials with similar design[3,18,19], to which complementary information can now be added. Weight loss occurs after gastrectomy in the early postoperative period, whereafter BW seems to be quite stable. It should be noted that when the present patients were reassessed 5 years after total gastrectomy, marginal weight loss was found, but when the two study groups were compared specifically a significant difference emerged in favour of those having a gastric substitute, who had weight gain. These effects were recorded without any obvious change in BCM[4]. This profound reduction in the BF compartment was maintained throughout the years after gastrectomy, again with a recovery observed only in patients allocated to have a gastric reservoir. Furthermore, the data on TSF thickness paralleled these results on BF compartments with a corresponding increase from 12 months after operation onwards in patients with a gastric reservoir. The clinical consequences of these observations have to be studied and elucidated further. The impact of fat loss on, for instance, functional parameters such as endurance[20] is warranted.

The fact that a decrease in lean body mass was observed during long-term follow-up was somewhat contradictory to early postoperative observations. However, when these changes were assessed in relation to ageing, no significant effect remained. Again no significant alterations were recorded in AMC, supporting the very limited effects on lean body mass after similar operations. These observations may also be of importance from a more general perspective, when different outcomes are compared in studies of the nutritional and metabolic consequences of different operative interventions in an ageing study population.

What are the mechanisms behind this long-term difference in weight control between patients having a simple Roux-en-Y oesophagojejunostomy and a gastric substitute? Although no significant difference was observed in nutritional intake between the operative procedures, there was a tendency towards an intake of larger meals in the reservoir group. In the early postoperative period, the authors have previously found no difference in food intake between patients having a gastric reservoir and those with a simple oesophagojejunostomy. On the contrary, 3 months after gastrectomy the former group complained more frequently of difficulties in consuming adequate amounts of food[3]. Apparently, a process of adaptation seems to be operating. In addition, a tendency towards lower faecal losses of energy was recorded in patients with a gastric reservoir. Taken together, it is reasonable to assume that the most likely mechanism behind weight gain in these patients is a marginal but, from the long-term perspective, improved food intake to which is added a minimal reduction in energy losses. Whether factors such as emptying of food from the reservoir[21–23] are of significance has to be clarified.

An issue that has been focused on is the importance of the duodenal passage for the functional outcome after gastrectomy. The largest controlled study with the longest controlled clinical follow-up hitherto presented is that by Fuchs and co-workers[19], who demonstrated no beneficial effects of reconstructing the duodenal passage by a jejunal interposition in addition to a gastric pouch compared with the widely used and technically less demanding Roux-en-Y reconstruction. These authors concluded that differences between the two reconstruction principles might be documented by sophisticated functional assessments, but are probably of no major clinical importance. Although others have claimed opposing opinions[5,24–27], it has to be emphasized that there are inherent methodological problems in a single-institution study designed to evaluate a specific type of reconstruction which, in addition, has been developed at that institution.

It can thus be concluded that pouch reconstruction on a Roux-en-Y limb after total gastrectomy has long-term clinical advantages with respect to weight gain, which are probably the result of slight, but in the long-term perspective potentially important, differences in food intake and faecal energy losses. Therefore, in patients with a favourable tumour stage, which suggests a chance for long-term survival, pouch reconstruction after total gastrectomy ought to be considered seriously.

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Relation between tumour necrosis factor α and interleukin 1β producing capacity of peripheral monocytes and pulmonary complications following oesophagectomy

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Background Adult respiratory distress syndrome and pneumonia remain a significant cause of morbidity and death following oesophagectomy. The aim of this study was to clarify the association between tumour necrosis factor (TNF) α and interleukin (IL) 1β with these pulmonary complications.

Methods The *in vitro* TNF-α and IL-1β producing capacity of peripheral monocytes with or without lipopolysaccaride (LPS) and serum level of IL-6 was measured in 19 patients with oesophageal cancer before and after surgery and in ten age-matched controls.

Results Six patients had raised TNF-α and IL-1β producing capacity of monocytes without LPS both before operation and on the day after surgery. In these patients plasma elastase and serum IL-6 levels subsequently increased while the ratio of arterial partial pressure of oxygen to fraction inspired oxygen decreased, and they developed bilateral lung infiltration on chest radiography on days 3–7. Five of the six developed pneumonia compared with none of the remaining 13 patients ($P < 0{\cdot}05$).

Conclusion Pulmonary impairment and pneumonia following oesophageal surgery was associated with raised monocyte producing capacity of TNF-α and IL-1β. These markers may be valuable in the preoperative assessment of patients awaiting oesophagectomy.

Operative procedures for oesophageal malignancy are becoming increasingly more radical and extensive[1,2]. Sepsis and multiple organ failure, mainly resulting from pulmonary complications and anastomotic leakage, are the major causes of postoperative death[3,4]. Acquired failure in the host immune defence mechanism is associated with such infections[5]. The authors previously reported postoperative pulmonary infections associated with deficiencies in cellular[6] and humoral immunity[7] as well as with increases in polyclonal immunoglobulin and acute-phase protein levels[8].

The pathological states induced by exaggerated secretion of either proinflammatory cytokines or systemic inflammatory response syndrome (SIRS)[9] are assumed to be associated with severe complications following oesophageal surgery. Septic shock and acute lung injury are not uncommon after operation. Tumour necrosis factor (TNF) α and interleukin (IL) 1β play a major role in the pathogenesis of SIRS[10,11]. These cytokines are produced mainly by monocytes[12,13] following surgical trauma or infection. The exaggerated secretion of TNF-α and IL-1β is mediated, in part, through the excessive induction of IL-8[14,15]. This activates neutrophils[16] to generate elastase[17] and reactive oxygen radicals[18], thus leading to tissue damage[14,15].

In the present study, to clarify whether TNF-α and IL-1β are associated with pulmonary impairment and pneumonia following oesophageal surgery, *in vitro* TNF-α and IL-1β producing capacity of peripheral monocytes as well as serum level of IL-6 were measured in patients undergoing transthoracic subtotal oesophagectomy.

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Patients and methods

Patients

The study included 19 patients with squamous cell carcinoma of the oesophagus. There were 15 men and four women, of mean age 63 years (range 55–84) years. Seventeen had a one-stage operation in which an oesophagectomy and oesophageal reconstruction was done simultaneously. The remaining two had a two-stage operation in which an oesophageal reconstruction was done approximately 1 month after oesophagectomy[19].

The operation consisted of a total intrathoracic oesophagectomy and mediastinal lymphadenectomy carried out through a right thoracotomy. After returning the patient to the supine position, the stomach or colon was prepared for reconstruction and an abdominal lymph node dissection done through a laparotomy incision. Simultaneously, isolation of the cervical oesophagus and neck node dissection was conducted through a collar incision. Finally, the stomach or colon was brought up by way of the subcutaneous or substernal route and an anastomosis was performed in the neck. The lymph nodes that were removed included the paratracheal, hilar, tracheobronchial, pretracheal, subaortic, paraoesophageal, posterior mediastinal and diaphragmatic nodes in the mediastinum, pericardiac, lesser curvature and coeliac nodes in the abdomen and supraclavicular, deep cervical, paraoesophageal and paratracheal nodes in the neck. When a two-stage operation was performed, subtotal oesophagectomy, mediastinal node dissection and oesophagocutaneostomy were performed initially while oesophageal reconstruction along with a cervical and abdominal node dissection was done in the second stage. General anaesthesia was used in combination with a thoracic epidural (T7/8) in every patient.

Before operation, 13 patients with malnutrition received total parenteral nutrition and two with local cancer invasion to surrounding organs underwent radiation therapy. The stage of oesophageal cancer was estimated according to the fourth edition of the *TNM Classification of Malignant Tumours* of the Union Internacional Contra la Cancrum[20]. Ten healthy elderly volunteers (six men and four women; mean age 77 (range 69–82) years) served as controls.

Blood collection

Venous blood samples (30 ml) were taken and 2–3 ml whole blood was used for measuring routine blood parameters including leucocyte count and C-reactive protein (CRP) levels. The serum was separated and stored at − 70°C pending analysis of TNF-α, IL-1β and IL-6 levels. Cold-spun plasma was prepared in sterile tubes containing ethylenediamine tetra-acetic acid (EDTA, 0·34 mmol/l) and stored at − 70°C for an elastase assay. Some 20 ml heparinized blood obtained in a sterile tube was immediately used for monocyte preparation.

Monocyte isolation

The heparinized blood was overlayed on Ficoll–Hypaque (Pharmacia Biotech, Uppsala, Sweden) and centrifuged at 400*g* for 30 min. Interface cells were collected and washed three times at 200*g*, 4°C for 10 min in RPMI 1640 medium (Gibco, Grand Island, New York, USA) containing streptomycin 100 mg/ml. The cells were resuspended at $3–5 \times 10^7$ cells per ml in RPMI 1640 containing 10 per cent fetal calf serum (FCS; Gibco). The cells were allowed to adhere in a 100-mm plastic tissue culture dish (Falcon, Oxnard, California, USA) precoated with FCS. Non-adherent cells were removed by extensive washing with medium and adherent cells were obtained by treatment with 0·02 per cent EDTA for 15 min followed by gentle flushing in the presence of FCS. The purity of the adherent cell population, as assessed by non-specific esterase staining, routinely exceeded 95 per cent. The adherent cells were counted and the concentrations were adjusted to 5×10^5 cells per ml in medium with 10 per cent FCS and streptomycin.

Monocyte cytokine production

The adherent cells were dispensed into microtitre plates (Falcon, no. 3072) at a concentration of 1×10^5 cells per well in 200 ml of the same medium with FCS. The cytokine producing capacity of the monocytes was tested in a medium containing lipopolysaccaride (LPS) from *Escherichia coli* 0111; B4 L4130 (Sigma Chemical Company, St Louis, Missouri, USA) or in medium alone. To determine the LPS-induced cytokine producing capacity, LPS was added at a final concentration of 0·5 mg/ml. The plates with adherent cells were cultured for 24 h at 37°C in a humidified atmosphere containing 5 per cent carbon dioxide. Cell-free supernatants were collected and stored at − 70°C until testing.

Assay of tumour necrosis factor and interleukins

TNF-α and IL-1β were measured by enzyme-linked immunosorbent assay (ELISA) using commercially available human TNF-α and human IL-1β kits (Otsuka Pharmaceutical, Tokushima, Japan) while IL-6 was measured using a human IL-6 ELISA kit (Toray-Fuji Bionics, Tokyo, Japan). Each assay was performed in triplicate. The lower detection limit of the assay was 15 pg/ml for TNF-α and IL-1β, and 12 pg/ml for IL-6.

Assay of C-reactive protein and granulocyte elastase

Serum level of CRP was measured by rate immunonephelometry (automatic Immunochemistry Analyzer; Eiken Kagaku, Tokyo, Japan). Plasma level of granulocyte elastase was determined using a Merck Immunoassay PMN Elastase (Merck, Frankfurt, Germany).

Postoperative acute lung injury and pneumonia

Patients were managed using prophylactic mechanical ventilation in the intensive care unit for approximately 4–7 days following oesophagectomy. Their postoperative course was carefully monitored by regular analysis of blood counts, chest radiographs, sputum cultures and arterial blood gases. The criteria used for diagnosis of postoperative pulmonary complications[21] were as follows: (1) acute lung injury: ratio of arterial partial pressure of oxygen (PaO_2) to fraction inspired oxygen (FiO_2) less than 300 mmHg and bilateral lung infiltration on chest radiography; (2) adult respiratory distress syndrome (ARDS): PaO_2/FiO_2 less than 200 mmHg and bilateral lung infiltration; and (3) pneumonia: positive lung infiltration, fever above 38°C, leucocytosis above 10 000 per mm^3 and positive sputum culture.

Statistical analysis

Data were compared using either the unpaired Student's *t* test for continuous variables or χ^2 test (with Yates' correction or Fisher's exact test, as appropriate) for discriminant variables. Differences were considered to be statistically significant when the *P* value was less than 0·05.

Results

Preoperative monocyte cytokine producing capacity and serum cytokine levels

Mean(s.e.m.) TNF-α, IL-1β and IL-6 *in vitro* producing capacities of peripheral monocytes unstimulated with LPS (spontaneous producing capacity) in healthy age-matched volunteers were 21(7), 16(1) and 397(33) pg/ml respectively. For monocytes stimulated with LPS, the respective values were 4733(804), 6725(1116) and 129 254(13 730) pg/ml. TNF-α and IL-1β were not detected in the circulating venous blood. Serum level of IL-6 was 1·1(0·4) pg/ml.

In patients with oesophageal cancer, the spontaneous producing capacities of TNF-α (164(49) pg/ml), IL-1β (87(24) pg/ml) and IL-6 (13 989(1684) pg/ml) were significantly higher than those in the volunteers, while the LPS-stimulated producing capacities of TNF-α (6577(804) pg/ml), IL-1β (8535(906) pg/ml) and IL-6 (72 841(8371) pg/ml) were not. Serum IL-6 level (19(7) pg/ml) was also significantly higher in patients than in the healthy, age-matched volunteers ($P < 0{\cdot}01$).

Kinetics of monocyte cytokine producing capacities and serum cytokine levels

Fig. 1 shows the kinetics of the *in vitro* cytokine producing capacities of peripheral monocytes either unstimulated or stimulated with LPS, and serum IL-6 level following surgery. TNF-α and IL-1β spontaneous producing capacities were significantly raised on days 1–3 after operation and then recovered to preoperative levels on days 7–14. IL-6 spontaneous producing capacity was significantly reduced on postoperative day 1 and recovered thereafter. LPS stimulated producing capacity after surgery was raised for TNF-α but reduced for IL-6, similar to the spontaneous producing capacity; no changes were observed for IL-1β throughout the postoperative period.

TNF-α and IL-1β were not detected in the circulating venous blood after operation in any patient. Serum IL-6 was raised on days 1–7 after operation and then recovered.

Stratification of patients according to monocyte cytokine producing capacity

There was a statistically significant correlation between the spontaneous TNF-α and IL-1β producing capacities on day 1 after operation ($r = 0{\cdot}96$, $P < 0{\cdot}01$) (*Fig. 2*). Six patients had high producing capacities for these two cytokines. The patients were divided, based on their TNF-α and IL-1β spontaneous producing capacity the day after surgery, into two groups: six patients in group I with TNF-α 400 pg/ml or more and IL-1β 200 pg/ml or greater; 13 patients in group II with TNF-α less than 400 pg/ml and IL-1β less than 200 pg/ml. No correlation was found between the producing capacities of IL-6 and TNF-α or between those of IL-6 and IL-1β; nor was there a correlation between LPS-stimulated producing capacities.

Groups I and II were well matched for tumour staging and treatment (*Table 1*). The duration of operation and blood loss were similar in both procedures for the two patients who underwent a two-stage operation.

Comparisons of cytokine kinetics

Fig. 3 shows a comparison of the kinetics for TNF-α, IL-1β and IL-6 spontaneous producing capacities and serum IL-6 level between groups I and II. TNF-α and IL-1β producing capacities in group I were significantly higher than those in group II on admission ($P < 0.05$) and were also raised significantly on days 1–3 after operation ($P < 0.01$).

IL-6 monocyte spontaneous producing capacity and serum IL-6 was higher in group I than in group II on admission and after surgery. The difference for IL-6 spontaneous producing capacity of the monocytes was statistically significant on day 7 after operation, and for serum IL-6 on postoperative days 3–7, but not on admission or at any other time.

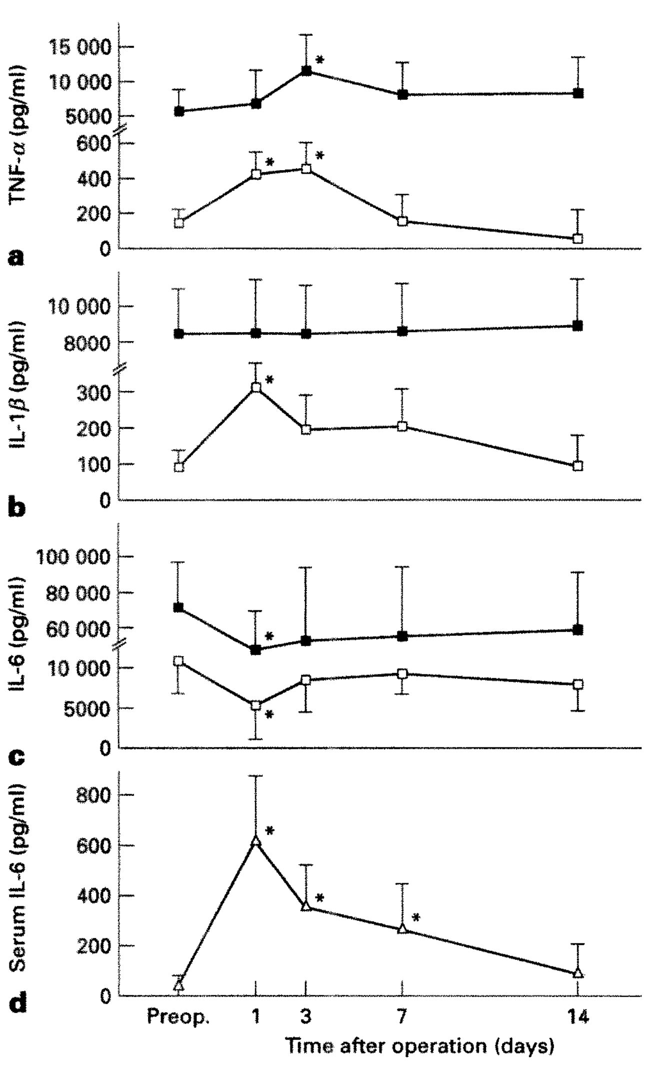

Fig. 1 Kinetics of cytokine producing capacities of monocytes (a–c) and of serum level of interleukin (IL) 6 (d) following oesophagectomy in all 19 patients, with (■) without (□) lipopolysaccharide. Values are mean(s.e.m.). TNF, tumour necrosis factor.* $P < 0.05$ *versus* preoperative level (Student's *t* test)

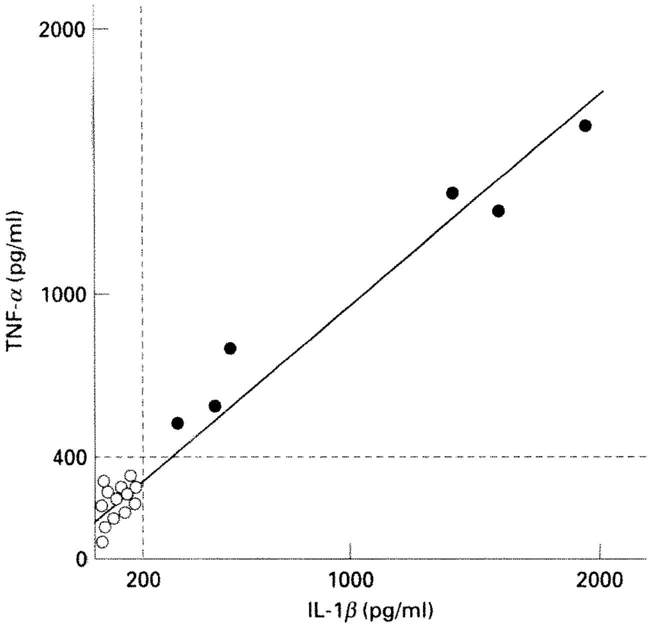

Fig. 2 Correlation between monocyte tumour necrosis factor (TNF) α and interleukin (IL) 1β spontaneous producing capacity the day after surgery. ●, Patients with TNF-α 400 pg/ml or more and IL-1β 200 or greater pg/ml (group I); ○, those with TNF-α less than 400 pg/ml and IL-1β below 200 pg/ml (group II). ($r = 0.96$, $P < 0.01$)

Table 1 Comparison of clinical details in patients grouped according to monocyte cytokine producing capacity

	Group I (*n* = 6)	Group II (*n* = 13)
Age (years)*	65(2)	62(2)
Sex ratio (M:F)	5:1	11:2
Tumour length (cm)*	6·8(1·8)	4·4(0·5)
TNM stage		
0, I, II	3	6
III, IV	3	7
Pulmonary function*		
Percentage vital capacity	110(6)	100(5)
Percentage FEV$_1$	78·0(1·9)	80·8(1·8)
Preoperative TPN	4	9
Preoperative radiation	1	1
Operative procedure		
One stage	6	11
Two stage	0	2
Duration of operation (min)*	713(66)	649(42)
Operative blood loss (ml)*	1503(86)	1063(141)

*Values are mean(s.e.m.). Group I, excessive monocyte cytokine producing capacity; group II, cytokine producing capacity not increased. TNM, tumour node metastasis; FEV$_1$, forced expiratory volume in 1 s; TPN, total parenteral nutrition

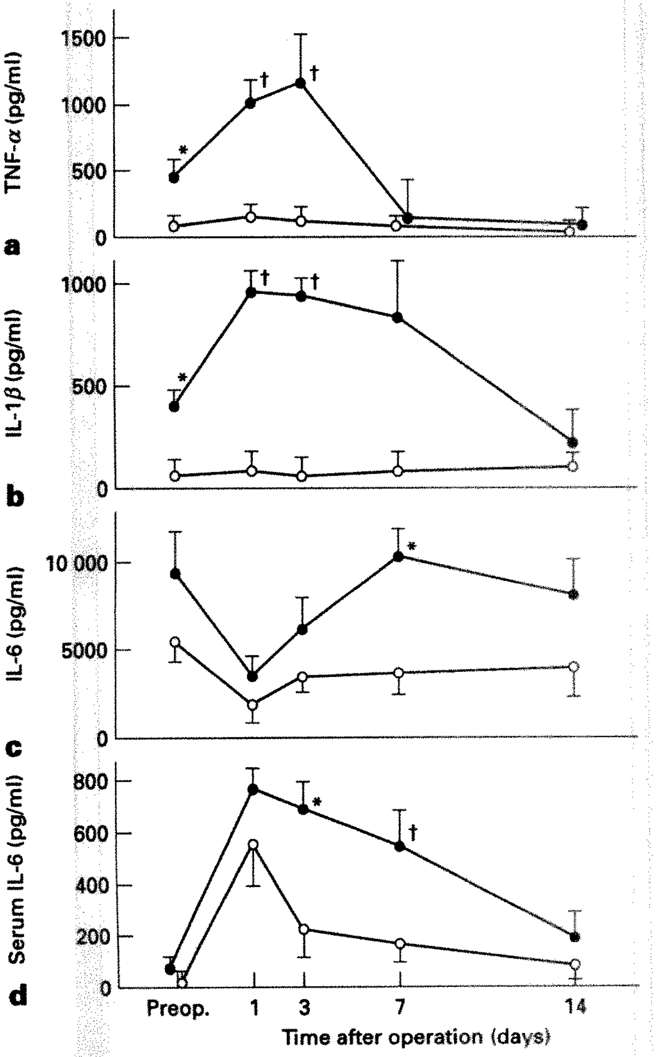

Fig. 3 Comparison of cytokine kinetics between group I (six patients; ●) and group II (13 patients; ○). a–c Spontaneous cytokine producing capacity of monocytes and d serum interleukin (IL) 6 level. Values are mean(s.e.m.). TNF, tumour necrosis factor. $^*P<0{\cdot}05$, $^\dagger P<0{\cdot}01$ *versus* group II (Student's *t* test)

LPS-stimulated monocyte cytokine producing capacities did not correlate with the spontaneous producing capacities. The TNF-α and IL-6 producing capacities were significantly depressed in group I compared with group II ($P<0{\cdot}05$) on admission and on postoperative days 1–7. In contrast, the IL-1β producing capacities were similar in both groups throughout the entire postoperative period (data not shown).

Plasma elastase, serum CRP and pulmonary kinetics

Fig. 4 compares kinetics of plasma elastase, serum CRP and PaO_2/FiO_2 following oesophagectomy in group I with those in group II. Plasma elastase level was raised on the day after operation and then recovered to preoperative level by day 14 in both groups. The level was higher in group I and significantly different from that in group II the day after surgery ($P<0{\cdot}05$). Serum CRP levels were raised after surgery but no significant difference was seen between the groups. PaO_2/FiO_2 decreased after surgery, but was lower in group I than in group II. The difference was significant 3 and 7 days after operation. PaO_2/FiO_2 reached a trough 7 days after operation in both groups. Mean PaO_2/FiO_2 was 203 mmHg in group I and 302 mmHg in group II on day 7.

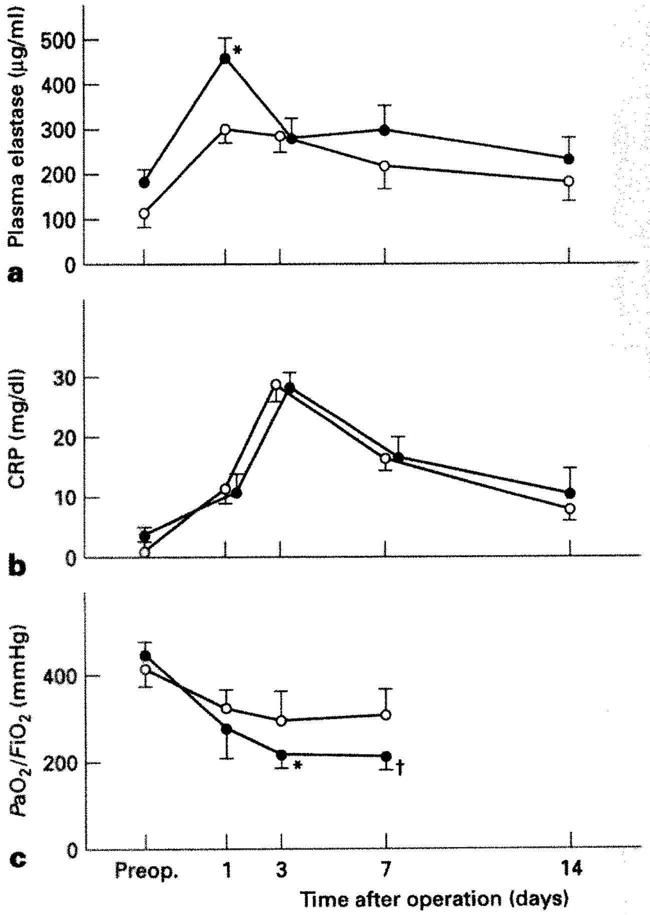

Fig. 4 Kinetics of a plasma elastase b serum C-reactive protein (CRP) and c ratio of arterial partial pressure of oxygen (PaO_2) to fraction inspired oxygen (FiO_2) in group I (●) and group II (○). Values are mean(s.e.m.). $^*P<0{\cdot}05$, $^\dagger P<0{\cdot}01$ *versus* group II (Student's *t* test)

Postoperative pulmonary complications

There were two patients with acute lung injury and four with ARDS in group I while five had acute lung injury and six had ARDS in group II. All patients in group I had pulmonary impairment, compared with 11 of 13 patients in group II. Pneumonia was associated with ARDS or acute lung injury in five of 19 patients, all in group I ($P<0{\cdot}05$). All patients recovered with intensive care.

Discussion

This study has shown an association between TNF-α and IL-1β and pulmonary complications following oesophageal surgery. *In vitro* the TNF-α and IL-1β producing capacities of peripheral monocytes greatly increased the day after surgery (TNF-α 400 pg/ml or more and IL-1β 200 pg/ml or greater) in six of 19 patients studied. This group also had significantly higher levels of plasma elastase on the day after operation and significantly higher levels of serum IL-6 and lower levels of PaO_2/FiO_2 with bilateral lung infiltration (acute lung injury and ARDS) on days 3–7. Excessively high producing capacities of TNF-α and IL-1β of peripheral monocytes *in vitro* the day after oesophagectomy appeared to be associated with subsequent pulmonary impairment. Five of these patients developed postoperative pneumonia, following acute lung injury or ARDS compared with none of the remainder.

Patients with excessively high capacities of TNF-α and IL-1β in their monocytes measured the day after operation also had significantly higher levels of these cytokine producing capacities before operation (TNF-α 200 pg/ml or greater and IL-1β 100 pg/ml or more) compared with the remaining patients. The reason for the priming of these monocytes remains unknown.

TNF-α and IL-1β are responsible for the induction of IL-6[22,23] which has many functions including the ability to induce the production of acute-phase proteins, in particular CRP, by hepatocytes[24,25]. After major surgical injury, serum IL-6 increases rapidly followed by an increase in serum CRP level[26,27]. The increase in serum IL-6 level following surgery is closely correlated with the duration of operation and blood loss[23,28]. Thus, an increase in serum IL-6 level following surgery is considered to reflect the production of TNF-α and IL-1β by monocytes. This is supported by the present study which showed that changes in the TNF-α and IL-1β producing capacities of peripheral blood monocytes *in vitro* are correlated with those in the serum IL-6. *In vitro* TNF-α and IL-1β producing capacities of monocytes seem to reflect the real production of these cytokines by monocytes *in vivo*, triggered by surgical trauma.

Several risk factors are associated with pneumonia following transthoracic oesophagectomy, including advanced age[29], smoking[30], chronic obstructive pulmonary disease[31], malnutrition[32], host immune defence impairment[5] and pulmonary dysfunction[29]. The present study showed in addition that acute lung injury and ARDS, induced by the overproduction of inflammatory cytokines, can lead to pneumonia following oesophageal surgery.

Preoperative TNF-α and IL-1β producing capacities of monocytes were significantly higher in patients who developed postoperative pneumonia. No association was observed for serum IL-6, plasma elastase or serum CRP before surgery. Preoperative TNF-α and IL-1β producing capacities in peripheral blood monocytes might be useful for predicting pulmonary complications following oesophageal surgery.

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Vascular Surgical Society of Great Britain and Ireland Abstracts

The following abstracts are from the papers presented at the 31st Annual Conference of the Vascular Surgical Society of Great Britain and Ireland, held in London, UK, on 26–28 November 1997. President of the Society, Professor Averil O. Mansfield, was in the Chair.

Abdominal aortic aneurysm repair: a 21-year experience

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Studies from other countries report that the operative mortality rate following abdominal aortic aneurysm (AAA) repair is declining, as is the proportion of patients operated as an emergency for symptoms and/or rupture. This may not be the situation in the UK. The results of infrarenal AAA repair in a single unit over 21 years (1976–1996) were reviewed by analysis of a prospectively gathered computerized database.

Some 492 patients (32·5 per cent) underwent elective repair of an asymptomatic AAA; 194 (12·8 per cent) elective repair of a symptomatic AAA; 156 (10·3 per cent) emergency repair of a symptomatic AAA; and 673 (44·4 per cent) repair of a ruptured AAA. There has been a tenfold increase in the number of repairs performed annually but no change in the proportion of patients in each group. The operative mortality rate was 6·1, 5·8, 14·1, and 37·0 per cent respectively and has increased in all four groups over the study. There has been a significant increase in age in those having elective surgery for asymptomatic AAA but not in the other groups.

This is the largest ever reported single-centre experience with infrarenal AAA repair. Disappointingly, it is still the minority who have elective surgery before the onset of symptoms and/or rupture. Despite surgical specialization, the operative mortality rate is increasing. This may be due to increasing patient age and comorbidity but is difficult to prove.

Survival after repair of ruptured aortic aneurysm: an anaesthetic view

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This study assessed the influence of a senior vascular anaesthetist on early survival following surgical repair of leaking abdominal aortic aneurysm (AAA).

The study was a retrospective audit of 150 consecutive ruptured AAAs repaired between January 1992 and November 1996. Outcomes were calculated, according to the three vascular and 23 non-vascular anaesthetists, at 10 and 30 days. Results are presented both for the group as a whole and for the 113 patients over 70 years of age.

One hundred and nineteen repairs were performed by one of the two consultant vascular surgeons and the remainder by senior trainees. The seniority of the surgeon did not influence outcome. In the over 70s the vascular anaesthetists achieved significantly better survival at 10 and 30 days. For the whole group this improved survival was only significant at 10 days.

Anaesthetist	No. of repairs	Mean age (years)	10-day survival	30-day survival
Over 70 years	113			
Vascular	54	77·0	39*	36*
Non-vascular	59	75·7	28	25
Whole group	150			
Vascular	69	74·6	49†	44
Non-vascular	81	73·0	45	41

$^*P<0{\cdot}01$, $^\dagger P<0{\cdot}05$ (χ^2 test)

It would appear that, as with surgery, there is a potential benefit for subspecialization in vascular anaesthesia.

Changing pattern of aortic aneurysm workload in a single centre following introduction of a programme of endoluminal repair

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A programme of endoluminal aneurysm repair was introduced in 1992 and its effect on workload was assessed by retrieving data for all patients undergoing surgical treatment of an infrarenal aortic aneurysm between February 1990 and January 1997. Operations were categorized as open, emergency, endoluminal (successful) and endoluminal (conversion).

Year	Open	Emergency	Endoluminal (successful)	Endoluminal (conversion)	Total
1990	62	10	—	—	72
1991	56	20	—	—	76
1992	44	22	0	5	71
1993	49	16	13	5	83
1994	62	17	40	4	123
1995	54	10	33	2	99
1996	48	10	43	2	103

There was a 48 per cent increase in workload from a mean of 73 operations in the first 3 years to 108 in the last 3 years, due predominantly to endoluminal cases. In 1996 open operations accounted for 47 per cent of the total and successful endoluminal procedures for 42 per cent, compared with 59 and 16 per cent respectively in 1993. The conversion rate fell from 100 per cent in the first year to 4 per cent in 1996.

The endoluminal programme has increased the number of aneurysms treated but has not altered significantly the number of open or emergency cases. With increased experience the endoluminal group now constitutes almost half of the elective workload at an acceptably low conversion rate.

Hidden hazards of blood transfusion during elective aortic aneurysm repair: a comparison of autologous and homologous products

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Cell-savers are increasingly used during aortic aneurysm (AAA) repair allowing autologous transfusion of red cells in saline. However, the infusate may contain other constituents of whole blood and inadvertent transfusion of activated neutrophils (PMN) (increased CD11b, CD18 expression, decreased L-selectin expression), proinflammatory cytokines (interleukin (IL)-1, IL-6, IL-8, tumour necrosis factor (TNF)α) and lipid mediators (leukotriene B_4, LTB_4) could promote a systemic inflammatory response syndrome. Levels of these mediators have been measured in ten patients during AAA repair, in the infusate from a cell saver and in 10 units of homologous packed cells.

	Patient	Infusate	Packed cells
WBC ($\times 10^9$ per litre)	5·55 (4·60–7·10)	5·65 (4·70–6·15)*	7·20 (5·90–8·55)†
Neutrophils ($\times 10^9$ per litre)	4·40 (3·38–5·42)	4·25 (4·05–4·95)	2·30 (0·75–3·55)*†
Monocytes ($\times 10^9$ per litre)	0·14 (0·09–0·16)	0·14 (0·10–0·21)	0·80 (0·60–1·40)*†
Lymphocytes ($\times 10^9$ per litre)	1·20 (0·91–1·32)	0·90 (0·62–1·65)	4·90 (3·60–6·20)*†
CD11b	160 (132–256)	538 (353–1131)*	875 (689–938)*
CD18	117 (105–131)	194 (148–228)	199 (153–210)*†
L-selectin	60 (47–62)	52 (35–75)	232 (157–241)*†
LTB$_4$ (pg ml^{-1})	7 (4–11)	264 (129–480)*	56 (36–164)*†
IL-6 (pg ml^{-1})	20·15 (17·75–24·85)	39·05 (24·25–100)*	4·65 (4·60–5·00)*†
IL-8 (pg ml^{-1})	1·00 (0·25–3·00)	10·50 (5·10–27·05)*	14·00 (9·65–26·00)*

Values are median (interquartile range). Negligible levels of IL-1 and TNF-α were detected. WBC, white blood cells. *$P<0\cdot0001$ *versus* patient, †$P<0\cdot0001$ *versus* infusate

The results confirm that the cell-saver infusate contains activated PMN (CD11b, CD18, L-selectin), monocytes and lymphocytes, and increased levels of LTB$_4$, IL-6 and IL-8. Although the transfusion of these cellular and biochemical factors could be detrimental the biological significance of this potential insult requires further assessment. Since similar results were obtained from homologous packed cells (with greater numbers of cytokine producing monocytes and lymphocytes) the other clinical advantages of autologous blood transfusion favour continued use of cell-saver devices.

Transferring patients with ruptured abdominal aortic aneurysm to a regional vascular surgery unit does not prejudice outcome

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It is not known whether having to transfer patients with ruptured abdominal aortic aneurysm (AAA) prejudices outcome. The aim of this study was to examine the relationship between transfer distance and outcome.

Transfer distance was defined as the road distance between this regional vascular unit and the patient's residence. Unit data were obtained from a prospectively gathered computerized database. Population data for this catchment area (population 1·2 million; area 4500 square miles) were obtained from the Information and Statistics Division (ISD) of the National Health Service.

Between 1 January 1989 and 31 December 1995, 972 patients with ruptured AAA were identified by the ISD. Of these 214 patients (23 per cent) were certified dead in the community, 551 (57 per cent) were certified dead in hospital and 202 (20 per cent) survived. Of 381 patients transferred to this unit, 316 operated patients travelled significantly further (median 6·9 (range less than 1 to 39) miles) than 65 non-operated patients (median 3·1 (range less than 1 to 36) miles) ($P=0\cdot0001$, Mann–Whitney U test). Of 316 operated patients, there was no significant difference in transfer distance between 188 (59 per cent) who survived (median 5·5 (range less than 1 to 31) miles) and 128 who died (median 5·5 (range less than 1 to 29) miles) ($P=0\cdot9$).

Only 39 per cent of patients known to have a ruptured AAA were transferred to this regional vascular unit. However, there was no significant difference between transfer distance and operative mortality rate in these patients. These data suggest that transferring patients with a ruptured AAA to a regional vascular unit does not appear to prejudice outcome.

Abdominal aortic aneurysm wall compliance and future risk of rupture: a preliminary analysis

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Abdominal aortic aneurysm (AAA) compliance, as determined by the pressure-strain elastic modulus (Ep) and stiffness (β), may be related to size, growth and risk of rupture. The relationship between AAA compliance and clinical outcome was determined.

Compliance was measured using an echo-tracking device (Diamove, Teltec, Lund, Sweden). Patients with a non-operated asymptomatic AAA ($n=112$), recruited from five different centres, underwent a single baseline compliance measurement and were followed for a median of 7 (range 2–18) months.

Seven patients ruptured their aneurysm and 16 underwent operative repair for non-ruptured AAA (two because of the onset of symptoms; 14 because of an increase in size). Ruptured AAAs had a lower Ep and β (*Table*) but there was no correlation between compliance and aneurysm size.

	Rupture ($n=7$)	Operated non-rupture ($n=16$)	Not operated or ruptured ($n=112$)	P value*
Diameter (mm)	54·9 (46·9–72·0)	49·2 (42·4–70·3)	45·0 (28·8–77·2)	<0·01
Ep (N m^{-2})	2·16 (1·59–3·72)	2·45 (1·22–7·58)	2·79 (0·55–9·46)	<0·01
β	15·0 (9·1–23·0)	17·3 (9·9–51·5)	18·2 (4·0–71·6)	<0·01

Values are median (range). *Kruskal–Wallis non-parametric analysis of variance three column comparison of median values

Preliminary data from this multicentre, prospective study suggest that AAA compliance measurements may be able to provide a more precise estimate of rupture risk than size or growth rate alone.

Value of atherosclerotic plaque characterization in balloon angioplasty of lower limb arteries

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Balloon angioplasty plays an important role in current treatment of peripheral arterial disease and its major limitation is restenosis. The effect of plaque morphology on angioplasty outcome was assessed.

Thirty patients (20 men, ten women; mean age 63 (range 53–85) years) with peripheral arterial disease were treated by angioplasty. Patients were scanned by Acuson duplex imaging. Computer-assisted image analysis was used to determine the mean pixel value (MPV) of grey scale of plaque. Lesion echogenicity was classified into: grade 1, less than 50 MPV (soft lesion); grade 2, 50–150 MPV (mixed lesion); and grade 3, more than 150 MPV (fibrocalcified). Arteries were scanned and images analysed 24 h before angioplasty and 24 h and 3, 12, 36, 52 and 65 weeks after angioplasty.

Forty-two lesions were examined (18 iliac, 24 femoropopliteal). Of 18 iliac lesions, four were grade 1, 12 grade 2 and two grade 3. In 24 femoropopliteal lesions five were grade 1, 16 grade 2 and three grade 3. All grade 1 lesions reoccluded at 3–12 weeks while at 36 weeks 80 per cent of grade 2 lesions and 60 per cent of grade 3 lesions did not show restenosis ($P<0\cdot0001$). There was no association between restenosis and symptoms.

This study has shown that soft echolucent atherosclerotic plaque restenoses quicker than mixed or fibrocalcified plaque. Plaque characterization may be of value in predicting the outcome of angioplasty.

Effect of intraoperative leucodepletion on neutrophil count and activation and cytokine production following limb salvage surgery

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Neutrophils (PMNs) promote ischaemia–reperfusion injury and PMN depletion ameliorates the injury in animal models. In ten patients undergoing limb salvage surgery the effect of PMN depletion (double-lumen femoral venous catheter, extracorporeal circuit, leucocyte filter, flow rate 200 ml min^{-1} for 15 min) on PMN count, adhesion molecule expression (CD11b, CD18, L-selectin: PMN activation) and cytokine levels (interleukin (IL)-6, IL-8, tumour necrosis factor (TNF)α) has been assessed compared with those in ten controls, in peripheral (PER) and femoral (FEM) venous blood at baseline (T_0) and 4 h (T), 24 h (T_{24}), 3 days (T_{3D}) and 6 days (T_{6D})after reperfusion.

PMN counts in filtered blood fell from 4·04 (range 2·55–5·75) to 0·72 (range 0·42–1·30) × 10^9 per litre ($P = 0·002$) and 1·08 (range 0·10–1·89) × 10^9 per litre ($P = 0·012$) after 5 and 15 min of filtration. PMN adhesion molecule expression was always lower in patients undergoing filtration (FEM and PER; significant to T_0 FEM ($P < 0·0001$), T_4 PER ($P = 0·0195$), T_{24} FEM ($P = 0·0012$) and T_{3D} ($P = 0·0140$) for CD11b, in T_0 PER ($P < 0·0001$) and T_{24} FEM ($P = 0·0311$) for CD18, and in T_4 PER ($P = 0·0072$) for L-selectin). Similarly filtration reduced IL-6 levels (all FEM and PER; significant at T_0 FEM and T_0 PER ($P = 0·0001$), T_{3D} ($P = 0·0256$) whilst TNF-α levels were higher, particularly in T_0 PER and T_4 PER ($P = 0·0001$). Finally, IL-8 levels were lower in PER samples (T_0, T_{24}; $P = 0·0001$) but higher in FEM samples (T_4, T_{24}; $P = 0·0001$).

This study suggests that PMN depletion in humans results in cellular (PMN activation: decreased levels of CD11b, CD18) and biochemical (decreased IL-6 level: reduced PMN-dependent cytokine; increased IL-8 level: inhibits PMN adhesion, perhaps via decreased L-selectin; increased TNF-α: inhibits PMN release) changes that should ameliorate ischaemia–reperfusion injury. The technique appears safe and is worthy of further investigation.

Increased proteolytic activity in acute carotid plaques

I. M. Loftus, S. Goodall, M. Crowther, L. Jones, P. R. F. Bell, A. R. Naylor and M. M. Thompson, *Leicester Royal Infirmary, Leicester, UK*

It is now generally accepted that acute changes in the atherosclerotic plaque are a prelude to the onset of clinical syndromes including stroke and myocardial infarction. There remains uncertainty about what causes this sudden change from a stable to an unstable plaque. Proteolytic enzymes (matrix metalloproteinases (MMPs)) have been implicated in previous studies. The aim of this study was to establish the character, level and expression of MMPs in carotid plaques and to correlate proteolytic activity with clinical status, spontaneous cerebral embolization and plaque histology.

Carotid plaques were obtained from 75 consecutive patients undergoing endarterectomy. Patients were divided into four groups according to symptomatology (group 1, asymptomatic; group 2, transient ischaemic attack/stroke/amaurosis fugax over 6 months; group 3, symptoms between 1 and 6 months; group 4, symptomatic within 1 month). All patients underwent preoperative and intraoperative transcranial Doppler (TCD) monitoring. Carotid plaques were collected and subjected to histological examination and quantification of MMPs.

	Group 1 ($n = 20$)	Group 2 ($n = 16$)	Group 3 ($n = 18$)	Group 4 ($n = 21$)
MMP-9 (ng)	31·5*	30·5*	30·6*	125·7*
Patients with emboli (TCD)	2	1	7	13
Rupture on histology	2	1	5	8

Values are median. *$P = 0·003$ (Kruskall–Wallis test)

There was no significant difference between the groups in MMP-1, -2, or -3, nor in the serum levels of all subtypes. The MMP-9 concentration was significantly higher in plaques undergoing spontaneous embolization ($P = 0·019$). Reverse transcriptase–polymerase reaction and *in situ* hybridization demonstrated higher levels of RNA for MMP-9 in highly symptomatic plaques which was localized to macrophages.

The concentration, production and expression of MMP-9 is significantly higher in unstable plaques.

Relationship between clinical grade of venous disease and calf perforating vein physiology

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Subfascial endoscopic perforator surgery has rekindled the controversy regarding the role of calf perforating veins in the pathogenesis of chronic venous insufficiency. The relationship between grade of venous disease and calf perforating vein physiology was determined.

The following groups were studied: grade 0, 50 limbs with no clinical or duplex evidence of venous disease; grade I, 95 limbs with varicose veins only; grade II, 58 limbs affected by lipodermatosclerosis but not ulcer; and grade III, 108 ulcerated limbs. Duplex imaging was used to determine the number, diameter and blood flow within calf perforating veins.

Incompetent perforating veins (IPV) which permitted bidirectional flow were significantly wider (median 4 (range 1–8) mm) than competent, unidirectional flow perforators (median 2 (range 1–6) mm) ($P < 0·01$, Mann–Whitney U test). The relationships between clinical grade and perforator characteristics are shown.

	Grade 0 ($n = 50$)	Grade I ($n = 95$)	Grade II ($n = 58$)	Grade III ($n = 108$)
No. of limbs with perforators*	44 (88)	90 (95)	57 (98)	106 (98)*
No. of limbs with IPV*	3 (6)	49 (52)	48 (83)	97 (90)†
Median (i.q.r.) no. of perforators per limb	1 (1–2)	2 (1–3)	2 (1–3)	2 (2–3)‡
Median (i.q.r.) no. of IPV per limb	0 (0–0)	1 (0–2)	1 (1–2)	2 (1–2)‡
Median (range) perforator diameter (mm)	2 (1–4)	3 (1–8)	4 (1–11)	4 (1–8)‡

Values in parentheses are percentages. i.q.r., interquartile range; *$P < 0·05$, †$P < 0·001$ (χ^2 test), ‡$P < 0·001$ (Kruskal–Wallis test)

Deteriorating clinical grade of venous disease is associated with an increasing number and diameter of medial calf perforating veins, particularly those permitting bidirectional flow.

Sympathetic nervous system in peripheral vascular disease: a response sensitive to local tissue ischaemia

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Lower limb venous pressure increases on dependency, stimulating a local sympathetic axon reflex and precapillary vasoconstriction. The resulting decrease in arterial calf inflow, known as the venoarteriolar response (VAR), is impaired in severe limb ischaemia. The effect of (1) early symptomatic peripheral vascular disease (PVD) and (2) tissue reperfusion following successful revascularization on this orthostatic reflex was examined.

The following patients were studied: group 1, 25 normal subjects; group 2, 25 patients with stable intermittent claudication due to infrainguinal PVD; and group 3, 25 patients with severe femoropopliteal PVD who had successful infrainguinal revascularization. All patients with PVD underwent angiography or duplex imaging, and all groups performed a treadmill test. Median resting ankle : brachial pressure index was 0·60 in group 2; in group 3 it was 0·42 before and 0·97 after revascularization. Laser Doppler fluxmetry measured the foot skin blood flux in the horizontal (HBF) and sitting (SBF) positions, and the VAR was calculated as (HBF − SBF)/HBF × 100 per cent. The pressure that elicits the reflex (pVAR) was calculated by inflating a pressure cuff over the distal calf to 60 mmHg to obtain sitting flux and deflating at increments until the skin flux rose.

	VAR (percentage postural flux change)	pVAR (mmHg)
Group 1	59 (51–67)*	45 (42–52)†
Group 2	30 (23–35)‡	22 (20–32)‡
Group 3	64 (56–72)	40 (35–42)

Values are median (interquartile range). $^*P = 0{\cdot}09$ *versus* group 3, $^{\dagger}P = 0{\cdot}01$ *versus* group 3, $^{\ddagger}P < 0{\cdot}0001$ *versus* groups 1 and 3 (Mann–Whitney *U* test)

Patients with claudication had significant impairment of the orthostatic response compared with normal subjects. After successful revascularization, and in spite of the extensive disease, this response returned to normal. Reperfusion increases tissue flow and decreases ischaemia, but does not alter the severity of atherosclerosis. The impairment of the orthostatic response is a result of tissue ischaemia, not the underlying pathology.

Colonoscopy with biopsy after aortic surgery: a unique study of the incidence of colonic ischaemia

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Colonic ischaemia is a well documented complication of abdominal aortic reconstruction. In this prospective study all patients had routine preoperative and postoperative colonoscopy and biopsy to determine the true incidence and implications.

Fifty-six patients undergoing elective infrarenal aortic surgery, 28 for aneurysm and 28 for occlusive disease, were studied before operation and 1 week after operation.

All patients had normal macroscopic and microscopic appearances on preoperative biopsies. A 30 per cent incidence of postoperative colonic ischaemia was identified by histology (16 of 53 patients), almost half (seven of 16) had normal macroscopic appearances. Two factors exhibited a statistically significant association with development of ischaemia: prolonged cross-clamp time (mean 45 *versus* 35 min; $P < 0{\cdot}05$, Mann–Whitney *U* test) and postoperative diarrhoea (88 *versus* 13 per cent, $P < 0{\cdot}005$, Fisher's exact test). Co-morbidity was much higher in patients with ischaemia (81 *versus* 13 per cent; $P < 0{\cdot}005$, Fisher's exact test). Overall morbidity was significantly greater in the aneurysm group (46 *versus* 21 per cent, $P < 0{\cdot}05$, Fisher's exact test).

Colonic ischaemia after aortic reconstruction is more common than previously reported and, although mild and transient in many cases, is still associated with significant morbidity. When suspected, colonoscopy with biopsy is recommended.

Influence of systemic factors and pre-existing venous intimal hyperplasia on the outcome of infrainguinal arterial reconstruction with vein

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The relevance of raised serum lipoprotein (a), fibrinogen and homocysteine levels and the presence of pre-existing venous intimal hyperplasia (IH) to development of vein graft stenosis (VGS) has been disputed. This study investigated the association between these plasma factors, IH and outcome.

Lipoprotein (a), fibrinogen and homocysteine were measured in each patient and a vein biopsy taken. Pre-existing IH was graded semiquantitatively (0, no IH; I, mild; II, moderate; III, severe). Patients underwent duplex graft surveillance following femorodistal bypass.

Sixty-three grafts in 56 patients were recruited. Forty-seven were available for follow-up (mean postoperative follow-up 15 (range 5–34) months). Patients with no pre-existing IH had significantly lower homocysteine levels than those with IH ($n = 50$, $P = 0{\cdot}036$, Mann–Whitney *U* test), but significantly higher lipoprotein (a) levels ($n = 50$, $P = 0{\cdot}012$, Mann–Whitney *U* test). Twenty-four of the 47 grafts developed a VGS. There was no association between VGS and age, sex, diabetes or level of reconstruction. Mean serum fibrinogen was higher, although not significantly, in those with VGS (4·16 *versus* 3·18 g l^{-1}; $n = 45$, $P = 0{\cdot}09$, Mann–Whitney *U* test). Grafts with grade II or III IH were significantly more likely to stenose than those with grade 0 or I ($n = 40$, $P < 0{\cdot}01$, χ^2 test). There was a highly significant association between patients with grade II/III IH and/or raised fibrinogen and VGS ($n = 38$, $P < 0{\cdot}005$, χ^2 test).

Plasma homocysteine levels correlate with the presence of pre-existing IH, which itself correlates with subsequent VGS. There is a marked relationship between the presence of raised plasma fibrinogen levels and pre-existing IH with the development of VGS. These investigations may allow early identification of grafts requiring intense surveillance.

Vein graft aneurysms: conclusive proof of a systemic process

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Although aneurysms are localized dilatations of the arterial wall, the question remains whether they are a focus of a generalized systemic disease process. There is evidence that extracellular matrix degradation secondary to matrix metalloproteinase (MMP) production forms the basis for aneurysm development. This study compared the risk of spontaneous aneurysm formation in vein grafts performed for aneurysms or occlusive disease.

Infrainguinal vein grafts performed during 1990–1995 were entered into a prospective audit and graft surveillance programme. Aneurysmal change was defined as a focal increase in graft diameter of greater than 1·5 cm (excluding false aneurysms and dilatation following graft angioplasty).

During the study, 221 grafts were performed in 200 patients for occlusive disease, while 24 grafts were performed in 21 patients for popliteal aneurysms. Graft surveillance revealed spontaneous aneurysm formation in ten of 24 grafts (nine patients) for aneurysm disease, but only four of 221 grafts (four patients) for occlusive disease ($P < 0{\cdot}001$, χ^2 test). To determine possible aetiological agents responsible for these results, long saphenous vein was harvested from patients undergoing bypass surgery and subjected to histological and biochemical analysis. Quantitative analysis of MMPs has revealed a twofold increase in the levels of MMP-2 and MMP-9 in patients with popliteal aneurysms compared with levels in patients with occlusive disease.

This study provides evidence that aneurysmal disease is a systemic process, possibly related to primay overexpression of MMPs within vascular tissue.

Minimally invasive long saphenous vein harvest

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One of the disadvantages of infrainguinal bypass grafting using the long saphenous vein is the morbidity associated with the long incision required. A new technique has been devised in an attempt to reduce this morbidity.

An incision was made over the distal portion of the artery to be grafted on to, and a segment of long saphenous vein isolated via this incision. An Ethicon R subcu-retractor was passed proximally and subcutaneously over the length of the vein traversing up to the saphenofemoral junction. All side branches were clipped with an endoscopic clip applicator and cut with laparoscopic scissors. A standard infrainguinal incision was made to expose the femoral artery, the vein divided was at the saphenofemoral junction. Over 4 months ten primary infrainguinal bypasses have been performed using an endoharvested vein; these have been compared with operations in a similar group of sex- and age-matched controls using the standard technique. Mean(s.d.) operating time was 213(102) min for endoharvest *versus* 145(68) min for conventional harvest. Total wound length was 16(9) cm and inpatient stay 5(3) days for the endoharvested group compared with 39(13) cm ($P < 0{\cdot}01$) and 10(12) days ($P < 0{\cdot}1$). Follow-up has been short (mean 12 weeks) but so far all grafts remain patent.

Endoscopic vein harvesting is a promising technique with operating time becoming shorter with practice. It has the advantages of reduced wound complications, better cosmesis and decreased inpatient stay.

Influence of interhospital transfer on survival of patients with ruptured abdominal aortic aneurysm

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Ruptured abdominal aortic aneurysm (AAA) is associated with a high hospital mortality rate. Often the reason for transferring a patient with a leaking AAA is the lack of an intensive care bed. It has been the authors' recent policy to accept all patients referred for repair of a ruptured AAA irrespective of their point of referral and availability of an intensive care bed.

Over 18 months 36 consecutive patients undergoing surgery for ruptured AAA were analysed.

Only 12 of the patients were primary referrals and the remaining 24 were referred from other hospitals. There was no significant difference in systolic blood pressure or haemoglobin concentration in either group. Six patients died perioperatively. Of the 30 survivors, 21 were transferred straight to the intensive care unit at this hospital and nine were transferred to another hospital. Patients transferred to other intensive care units were returned back when they were extubated and fit for transfer. Four of the 12 local patients died compared with 11 of 24 patients referred from other hospitals (*P* not significant). Of those initially transferred to another hospital's intensive care unit after surgery, two of nine died. There were no deaths in transit.

This study of ruptured AAA demonstrated that reasonable results can be obtained following interhospital transfer. Patients can be transferred safely once the procedure has been performed.

Prevalence of cerebral infarcts in relation to severity of carotid disease in the asymptomatic carotid surgery trial

P. Robless, on behalf of the ACST collaborators

In the Asymptomatic Carotid Surgery Trial (ACST) over 1630 patients have been randomized to determine if carotid endarterectomy (CEA) prolongs stroke-free survival compared with best medical treatment alone. Carotid duplex scanning is used to determine degree of stenosis and plaque echolucency. This study aimed to assess the prevalence of cerebral infarcts in relation to severity of carotid disease.

Patients with preoperative computed tomography (CT) were included. Those with previous contralateral CEA were excluded. Patients were divided into those with (1) bilateral carotid stenoses greater than 80 per cent, and unilateral stenosis greater than 80 per cent and 80 per cent or less and (2) those with more than 25 per cent and less than 25 per cent plaque echolucency.

Eight hundred and fifteen patients satisfied the criteria for the study giving 1630 vessels under consideration. All had information on degree of carotid stenosis by duplex scanning and 703 patients had infarction on plaque echolucency available. The prevalence of unexpected CT infarction was 23 per cent. Patients with bilateral carotid stenoses greater than 80 per cent (42 of 366) had the highest incidence of cerebral CT infarction (38 *versus* 23 per cent, $P = 0{\cdot}03$) compared with patients with unilateral stenosis above 80 per cent (324 of 366). Unilateral stenoses greater than 80 per cent (408 of 1630) had a higher incidence of ipsilateral CT infarct (18 *versus* 12 per cent, $P = 0{\cdot}002$) than unilateral stenoses of 80 per cent or less (1222 of 1630). Mantel–Haenszel test for linear association was significant in these groups ($P = 0{\cdot}03$). Those with greater than 25 per cent echolucent plaque showed no significant difference in the incidence of ipsilateral cerebral infarction.

In the ACST, bilateral carotid stenoses greater than 80 per cent had the highest incidence of cerebral infarction. Unilateral carotid stenosis greater than 80 per cent was associated with a higher incidence of ipsilateral cerebral infarcts on CT than unilateral stenosis of 80 per cent or less.

Training in abdominal aortic aneurysm surgery

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Reduction in juniors' working hours and 'Calmanization' of training mean operative experience must be gained more efficiently. The aim of this study was to examine training in abdominal aortic aneurysm (AAA) repair, a nationally agreed vascular 'indicator operation' as defined by the Royal College Confidential Enquiry into Surgical Training (1996).

The study was an analysis of a prospectively gathered, computerized database of 994 consecutive AAA repairs between 1987 and 1996.

Since 1991 consultants have trained juniors at a significantly higher proportion of elective cases ($P < 0{\cdot}03$, χ^2 test). There has also been an increase in the proportion of emergency cases at which the consultant was not scrubbed ($P < 0{\cdot}01$). The operative mortality rate did not change significantly during the study and was not significantly related to consultant role in theatre.

	1987–1991		1992–1996	
	Percentage of operations	Operative mortality rate (%)	Percentage of operations	Operative mortality rate (%)
Elective AAA repair				
Consultant operating	73	7	54	5016
Consultant assisting	20	7	32	11
Consultant not scrubbed	7	0	14	7
Emergency symptomatic AAA repair				
Consultant operating	69	9	50	16
Consultant assisting	19	11	24	11
Consultant not scrubbed	12	7	26	7
Ruptured AAA repair				
Consultant operating	73	36	56	34
Consultant assisting	16	27	20	25
Consultant not scrubbed	11	20	24	45

These data indicate that supervised trainees can perform an increasing proportion of elective and emergency AAA surgery without increasing the operative mortality rate. Towards the end of training, trainee surgeons can safely operate alone in selected cases. Such experience is appropriate and desirable in the months leading up to a consultant appointment.

Vascular radiological experience in vascular surgical trainees

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It is recommended that vascular surgical trainees should have experience in diagnostic angiography and interventional radiological procedures. There are no data available to indicate whether such experience is being obtained.

A postal questionnaire was sent to 76 specialist registrars (SpRs) who had declared a subspecialty interest in vascular surgery.

There were 54 replies (response rate 71 per cent) from SpRs in all 6 years of training. Twelve (22 per cent) wished to become pure vascular surgeons, 39 (72 per cent) vascular/general surgeons and two (4 per cent) wished to be vascular/transplant surgeons. One respondent was undecided. Forty-seven (87 per cent) felt a formal radiological training to be important and 48 (89 per cent) wished to have training in interventional radiological techniques themselves. Only 26 (48 per cent) had had any exposure to vascular radiological techniques, five through research (three on animals only and two solely in aortic stent grafts), three abroad (two by travelling fellowships and one by a European training) and three in other UK centres; only 15 had received any vascular radiological experience in their own hospital. In all but three cases the SpRs had arranged their own radiological training, mainly on an informal basis.

Vascular SpRs feel it important to have a training in vascular radiological techniques. Fewer than half of the respondents had received any such training and most had arranged it themselves. Formal vascular radiological training should become a requirement of all vascular surgery training schemes.

Cross-training in endovascular and vascular surgery

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To complete level 3 subspecialty training, vascular specialist trainees require experience in endovascular techniques. Such training would be desirable, but integrated programmes have yet to be instituted widely. This study reports a first year of experience of a programme designed to offer conventional surgical experience to radiologists and to train junior vascular surgeons in endovascular techniques.

The module adopted in this centre was for vascular surgical trainees to attend two lists in the interventional radiology suite per week and for a consultant radiologist to participate in one operating session, when appropriate. Neither of the radiology sessions was accompanied by radiology trainees and competition for cases therefore did not arise.

In the first year of this programme the higher surgical trainees performed 15 diagnostic arteriograms, 62 percutaneous angioplasties (PTAs) and insertion of one caval filter. The location of the PTA sites was iliac artery in 24 per cent, femoropopliteal in 43 per cent, crural in 19 per cent and vein graft in 14 per cent. Some 79 per cent of the interventions were intraluminal with the remainder being subintimal; 40 per cent were for occlusions. Twenty-eight endovascular aneurysm repairs were undertaken as joint surgical/radiological procedures in the operating theatre. During the same interval the consultant radiologist performed 30 femoral anastomoses and eight long saphenous high ties.

This integrated module of vascular training provides one system that facilitates training of both vascular surgeons and radiologists. It is likely that closer cooperation between radiologists and surgeons will be necessary in future and cross-training programmes should be mandatory.

Carotid duplex ultrasonography: can a variance of duplex methodology alter patient management?

S. Byrd, on behalf of the Asymptomatic Carotid Surgery Trial (ACST) collaborators

Carotid duplex ultrasonography, used in clinical practice since the 1980s, has replaced angiography as the first-line investigation for carotid stenosis. The aim of the study was to assess duplex methodology in 26 vascular laboratories used by 36 British surgeons in the Asymptomatic Carotid Surgery Trial. Specific attention was focused on areas which could significantly alter results such as: Doppler insonation angle, diagnostic criteria for determining degrees of stenosis and reporting process.

Routine vascular laboratory practice was evaluated by questionnaire. Respondents also submitted a copy of their individual diagnostic criteria and reporting form.

Results showed that 29 per cent used a standardized angle of 60°. A variable angle of 30°–60° was used by 71 per cent of respondents. Any change of Doppler angle will alter velocities within a given stenosis. For the 26 laboratories, there were more than 18 different individual criteria used for determining the degree of carotid stenosis. Findings were then reported as diameter reduction by 58 per cent, area reduction by 21 per cent and 17 per cent used both. To understand whether this variance could affect patient management, a single stenotic lesion was assessed by an independent sonographer. Doppler angle was varied at 50°, 60° and 70°. Resulting velocities were applied to individual laboratory diagnostic criteria. A predetermined cut-off point of 70 per cent was assigned to recommending possible surgical intervention. At a Doppler angle of 50°, four laboratories would consider this lesion as appropriate for surgery. At 60°, 13 laboratories would recommend surgery. At 70°, all laboratories indicated surgery.

Variance in carotid duplex methodology can change findings such that a patient's management may be altered. Further standardization of vascular laboratories will resolve this problem.

Is it time for a randomized trial of local *versus* general anaesthesia for carotid endarterectomy?

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Although carotid endarterectomy (CEA) performed under local anaesthesia (LA) allows optimum cerebral monitoring and maintains cerebral autoregulation it is suggested that hypertension and catecholamine release increase cardiac morbidity. A recent meta-analysis of non-randomized studies

(2070 LA, 3447 general anaesthesia (GA)) suggests that death (0·82 *versus* 1·16 per cent), stroke (1·98 *versus* 5·31 per cent) and myocardial infarction (MI) (0·6 *versus* 1·3 per cent) are less frequent in patients having LA.

In a prospective study 89 CEAs were performed under LA (superficial and deep cervical plexus block; 20 ml 0·5 per cent bupivacaine, 20 ml 1 per cent prilocaine) and 101 under GA (1 mg alfentanil, 0·5–2·0 per cent isoflurane, nitrous oxide/oxygen). Although non-randomized, patients had a free choice of the type of anaesthetic. The sex ratio (LA M:F 65:24; GA 57:44), mean age (67·9 *versus* 68·1 years) and history of ischaemic heart disease (31 *versus* 34 per cent), hypertension (66 *versus* 56 per cent), smoking (52 *versus* 64 per cent) and diabetes (11 *versus* 14 per cent) confirmed that the two groups were similar, as did the indications for surgery (LA *versus* GA: transient ischaemic attack 38 *versus* 38 per cent; cerebrovascular accident 33 *versus* 32 per cent; amaurosis 23 *versus* 25 per cent; asymptomatic 6 *versus* 5 per cent; presence of greater than 70 per cent bilateral stenoses 37 *versus* 35 per cent).

	Local anaesthesia ($n = 89$)	General anaesthesia ($n = 101$)
Shunted	15 (17)	67 (67)
Stump pressure <50 mmHg	46 (52)	67 (67)
30-day stroke rate	0 (0)	4 (4)*
Perioperative MI	1 (1)	3 (3)
Death	1 (1)	2 (2)

Values in parentheses are percentages. *$P = 0{\cdot}057$ *versus* LA; $P = 0{\cdot}046$ *versus* LA for combined stroke/MI

These results support the concept that all complications of CEA may be less frequent when surgery is performed under LA, and reinforce the need for a prospective, randomized trial.

Identification of the unstable carotid plaque

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The aim of this study was to determine the relationship between ultrasonographically evaluated carotid plaque echolucency, the degree of carotid stenosis on duplex imaging, the incidence of ipsilateral cerebral infarction on computed tomography (CT) and cerebrovascular symptoms.

One hundred and ten consecutive patients referred for the evaluation of carotid stenosis with 149 plaques, 59 symptomatic and 90 asymptomatic, having 50–90 per cent carotid stenosis were studied. Ultrasonographic images of the plaques were standardized by computer so that the grey scale median (GSM) of blood was 0–5 and of adventitia 180–200 on a linear scale 0–255 (interobserver variability, $r = 0{\cdot}93$). The GSM of the plaque was used as a measure of plaque echolucency. The stenosis was evaluated by duplex imaging, and the presence or absence of ipsilateral cerebrovascular symptomatology and CT infarction was noted.

GSM less than 45 and stenosis less than 70 per cent identified a group with a 34 per cent incidence of symptomatic plaques and 39 per cent incidence of plaques associated with ipsilateral cerebral CT infarction. GSM less than 45 and stenosis more than 70 per cent identified a group with incidences of 62 and 52 per cent respectively (high-risk group). GDM more than 45 and stenosis more than 70 per cent identified a group with corresponding incidences of 20 and 25 per cent, and GSM more than 45 and stenosis less than 70 per cent identified a group with incidences of 4 and 17 per cent respectively ($P < 0{\cdot}05$, χ^2 test).

These results indicate that computer-based plaque characterization and degree of stenosis can identify plaques at high risk of cerebral infarction and symptoms; aspects which have potential application in the management and natural history studies of carotid plaques.

S-nitrosoglutathione, a targeted nitric oxide donor, reduces embolization following carotid endarterectomy

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Cerebral embolism is the major cause of stroke, but current antiplatelet and antithrombotic medications are suboptimal. Assessment of new agents is limited by a lack of *in vivo* models in which to evaluate their action. Carotid endarterectomy (CEA) creates a thrombogenic surface by endothelial denudation. The authors have previously demonstrated frequent embolic signals in the ipsilateral middle cerebral artery (MCA) of patients following this procedure using transcranial Doppler ultrasonography, despite aspirin therapy. An *in vivo* model of cerebral embolization has been developed in which the action of S-nitrosoglutathione (GSNO), a targeted nitric oxide donor, has been tested.

Twenty-four patients (12 control, 12 GSNO) were recruited before CEA. All were pretreated with aspirin 300 mg daily for at least 1 week before surgery. Transcranial Doppler ultrasonographic recording from the ipsilateral MCA was performed for 3 h after operation. The GSNO group received intravenous treatment of 4·4 nmol kg^{-1} min^{-1}, commenced at induction of anaesthesia and continued for 2 hours from skin closure. All data were recorded to digital audio tape for later blinded analysis offline.

There was a significant reduction in the number of embolic signals detected during the 3-h period in the GSNO group: controls mean(s.d.) 59·58(61·54) (median 38·5); GSNO 12·42(16·63) (median 7·5) ($P = 0{\cdot}0078$, Mann–Whitney U test).

Significant platelet aggregation and embolization occurred despite aspirin therapy. The targeted nitric oxide donor, GSNO, reduced embolization rates. This model allows the efficacy of new antiplatelet and antithrombotic agents to be determined using small patient numbers.

Macrophage infiltration within the cap of carotid plaques predicts the onset of cerebral ischaemic symptoms

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Numerous studies have attempted to correlate clinical history with carotid plaque morphology but the mechanisms by which intraplaque factors precipitate the development of symptoms is largely undetermined. In coronary and aortic atherosclerotic lesions, macrophage infiltration of plaques, particularly within the cap and shoulder regions (SH), is associated with plaque instability.

Twenty-nine carotid endarterectomy specimens have been assessed using haematoxylin and eosin, Van Gieson and immunostaining with antimacrophage (HAM56) monoclonal antibody. Computerized planimetry was used to quantify the percentage area occupied by macrophages in the cap, SH and the entire sclerotic component (SC) of the plaques. These results were then correlated with the interval between the patient's last ipsilateral carotid territory symptoms and surgery.

Mean(s.e.m.) macrophage concentrations in the SC, SH and cap were 0·9(0·40), 1·57(0·31) and 2·52(0·46) per cent respectively (SC *versus* SH $P = 0{\cdot}03$; SC *versus* cap $P = 0{\cdot}002$; SH *versus* cap $P = 0{\cdot}0173$). While no relationship existed between the macrophage concentrations of the SC and the SH and the history of cerebral ischaemic events, there was a significant negative correlation between cap macrophage concentration and the time since the patient's last ipsilateral ischaemic symptom ($P = 0{\cdot}0177$).

Macrophage infiltration of plaques, particularly in the cap, may promote plaque instability and could be important in the pathogenesis of symptomatic cerebral ischaemia.

Is carotid endarterectomy a safe operation in the elderly?

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While the incidence of thromboembolic stroke increases with age, general practitioners are less likely to refer patients aged over 70 years for carotid endarterectomy (CEA) because of a perceived higher operative risk. To determine the validity of this assumption a prospective audit of the risk of death and/or stroke in elderly patients undergoing CEA was undertaken.

Two hundred and thirty-five consecutive CEAs were performed in patients aged 70 years or more (median age 75 (range 70–88) years) between January 1992 and July 1997. All had an ipsilateral stenosis of greater than 70 per cent, and one-third had contralateral occlusion or severe stenosis. Exclusion criteria for operation were a concurrent illness giving an anticipated survival of less than 2 years, dementia or an inability to maintain independent living. Endarterectomy was performed under normotensive normocarbic general anaesthesia with systemic heparinization, routine patching and shunting, and monitoring by transcranial Doppler and angioscopy. During this time 317 CEAs were performed in patients aged less than 70 years.

Patient age	No. of CEAs	Death/ disabling stroke	Death/ any stroke
40–69 years	317	9 (2·8)	14 (4·4)
70–90 years	235	6 (2·6)	9 (3·8)

Values in parenthesis are percentages

The commonest single cause of morbidity was postoperative thrombosis (six of nine patients).

These findings suggest that CEA can safely be performed in selected patients and that age alone should not exclude consideration for surgery.

Management and outcome of 50 carotid sheath tumours

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Between 1985 and 1997, 50 carotid sheath tumours in 45 patients were managed. Forty-five surgical excisions were undertaken in 39 patients of whom four had bilateral tumours. Median age at presentation was 43 (range 20–79) years and tumours were almost twice as frequent in women (female to male ratio 1·9:1). Previous exploration had been performed on 20 tumours.

Preoperative nerve deficits were present in five patients (three involving X and XII nerves, one IX, X and XII nerves, and one Horner's syndrome). Thirty-five tumours arose from the carotid body, seven from the vagus nerve, one was a glomus jugulare tumour and two were sympathetic schwannomas. Of the carotid body tumours, two had metastases and 34 were completely excised; 19 required external or internal carotid artery excision. Ten tumours were adherent to cranial nerves, resulting in four permanent XII nerve palsies. Of the patients with vagal tumours, one had neuroendocrine secretion. Two of these seven patients required excision of an involved XII nerve. Both schwannomas and the jugulare tumour were successfully excised. There was one death from a subarachnoid haemorrhage. At mean follow-up of 5·9 years, two tumours have recurred and required re-excision.

These data demonstrate that surgical excision of tumours within the carotid sheath can be undertaken with acceptable morbidity and mortality rates, and a low incidence of recurrence.

Early discharge after carotid endarterectomy reduces cost without increasing complications

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Reducing the cost of carotid endarterectomy (CEA) is important, but must not cause an increase in complications. A prospective audit of investigations, results, hospital care and surgical outcome was undertaken over 5 years to evaluate the procedure. A patient survey on early discharge was also performed.

Median length of stay has reduced from 7 to 2 days including one night before operation, saving £750 per procedure. Overnight observation in the intensive care unit was replaced in 1993 by 4 hours of observation in the recovery suite, saving £1500 per procedure. Since 1995, angiography was only used when duplex findings were unclear, saving £240 per procedure. Cerebral computed tomography has been restricted to patients presenting with stroke. Complication rates have not altered despite these changes. One patient was readmitted within 30 days. Over 80 per cent of patients were pleased with early discharge.

Year	Median stay (days)	Cost saving per CEA (£)	Stroke and death rate (%)	Total neurological events (%)	Other compli- cations	Re- admission within 30 days
1992	7	0	0 of 24 (0)	0 of 24 (0)	2	0
1993	5	1800	3 of 34 (9)*	3 of 34 (9)*	2	0
1994	3	2100	0 of 35 (0)*	0 of 35 (0)*	2	0
1995	2	2490	3 of 51 (6)*	4 of 51 (8)*	1	0
1996	2	2550	2 of 67 (3)*	2 of 67 (3)*	3	1
Total			8 of 211 (3·8)	9 of 211 (4·3)	10	1

Values in parenthesis are percentages. *P not significant *versus* 1992 (Fisher's exact test)

Discharge from hospital the day after CEA is possible in over 90 per cent of patients without an increase in early readmission or complications, and is a safe way of increasing the cost effectiveness of CEA.

Maintaining vascular services and staying out of the red

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In most Trusts, vascular activity forms part of the general surgical contract. The 'average specialty cost' of a surgical episode in this hospital is £880, considerably less than the real cost of treating a patient with arterial disease. Savings on minor surgery may compensate for this discrepancy as far as the contract with the local health authority is concerned. However, centres undertaking specialized tertiary referrals from surrounding health authorities under block contracts may find that this work constitutes a major 'loss leader'.

This vascular unit, which provides a tertiary service for a population approaching two million, had a shortfall on income for direct costs in 1995–1996 of £88,000. Surrounding purchasers were only prepared to negotiate on the basis of real additional costs incurred. The 'bottom up' costs of each case referred in during 1995–1996 were therefore calculated, including the cost of items such as minutes in theatre, radiology disposables, drugs, staff costs, length of stay, etc. This allowed accurate pricing of major vascular surgery such as ruptured aneurysm (£8702) and major emergency reconstructive surgery (£3436). On the basis of these costings an additional £100,000 of funding was secured from surrounding health authorities in the 1996–1997 contracting round. This has enabled the unit to cope with its previous overspend and has helped fund an additional consultant post.

Outpatient management of deep vein thrombosis

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Patients with deep vein thrombosis (DVT) conventionally receive inpatient treatment with up to a week of intravenous heparin and conversion to warfarin. This study assessed the efficacy and safety of treatment with subcutaneous low molecular weight heparin (tinzaparin) administered once a day to outpatients.

During 1995, 632 patients attended the accident and emergency department with a possible diagnosis of DVT. They were initially screened using light reflection rheography (LRR), a previously validated technique, and those suspected of DVT then proceeded to venography and in some cases duplex imaging as well. Some 427 patients were LRR negative. Of the 205 who proceeded to venography, 110 had a venogram that was negative for DVT and 95 had a positive venogram. Ninety-one patients were treated according to the protocol, 11 had malignant disease, four had thrombophilia and the rest (84 per cent) were idiopathic cases.

Patients were weighed and given appropriate doses of tinzaparin and warfarin, then discharged home with a prepackaged treatment kit containing syringes, tinzaparin, warfarin and an instruction sheet. A district nurse visited to perform the subsequent five daily injections. Patients attended the next anticoagulation clinic, held twice weekly, to have their warfarin dose monitored. There were no thrombotic or embolic complications in any patient. No bleeding occurred during the 5 days on tinzaparin although there were two episodes of minor bleeding on warfarin. Over 725 hospital bed days were released by the use of this regimen.

The outpatient management of DVT is effective and safe.

Relationship between sex, symptoms and signs of venous disease and the results of colour flow duplex scanning: a population-based study

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The relationship between sex, venous symptoms and signs, and duplex findings in the general population was defined. Some 1566 subjects (699 men, 867 women) aged between 18 and 64 years, randomly selected from the registers of 12 family practices, underwent an interview, clinical examination and colour flow duplex scanning of both legs.

Women were more likely to have a history of varicose veins (13 *versus* 7 per cent, $P<0{\cdot}01$, χ^2 test), phlebitis (4 *versus* 1 per cent, $P<0{\cdot}01$) but not leg ulcer (0 *versus* 1 per cent, $P<0{\cdot}01$); and to complain of leg heaviness/tiredness (26 *versus* 14 per cent, $P<0{\cdot}01$), swelling (20 *versus* 7 per cent, $P<0{\cdot}01$), ache (49 *versus* 28 per cent, $P<0{\cdot}01$) and cramps (38 *versus* 31 per cent, $P<0{\cdot}01$). However, on examination, women were less likely to have superficial varices (23 *versus* 32 per cent, $P<0{\cdot}01$), skin changes of chronic venous insufficiency (CVI) (5 *versus* 9 per cent, $P<0{\cdot}01$), or reflux exceeding 0·5 s in the femoral (4 *versus* 9 per cent, $P<0{\cdot}01$) and popliteal (8 *versus* 14 per cent, $P<0{\cdot}01$) veins. There was no difference with respect to superficial reflux. There was a weak association between symptoms, superficial varices and superficial (but not deep) venous reflux on duplex in women ($P=0{\cdot}05$). In men there was a significant association between symptoms and skin changes of CVI ($P<0{\cdot}01$), but not between symptoms and reflux on duplex imaging.

Although 'venous' symptoms are significantly more common in women, men have a higher prevalence of superficial and deep venous disease on clinical and duplex examination. There is an inconsistent correlation between 'venous' symptoms, examination and duplex findings, particularly in women.

Prevention of leg ulcer recurrence: a role for the vascular surgeon?

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Prevention of recurrent venous leg ulceration is a difficult and underestimated management problem. The aim of this study was to assess the influence of a vascular-led community ulcer service and venous surgery on long-term recurrence rates.

Vascular-led community clinics were introduced in 1995 with a one-stop assessment including ankle:brachial pressure index and venous duplex imaging. Patients were treated with compression bandaging and venous surgery was advised if superficial venous disease alone was detected. All healed patients received compression hosiery and were reviewed every 3 months. Recurrence at 6 and 12 months in all healed ulcers was recorded in 1994 and again in 1996 after introduction of the vascular-led clinics.

Vascular-led ulcer clinics reduced 6-month recurrence rates from 42 to 13 per cent and 1-year recurrence rates from 48 to 15 per cent ($P<0{\cdot}01$). Venous surgery further reduced 1-year recurrence from 20 to 5 per cent ($P<0{\cdot}05$). Ulcer recurrence was higher in the first 6 months compared with the second 6 months after healing ($P<0{\cdot}01$).

	Before ulcer clinics (1994)	Ulcer clinics (1996)	Ulcerated limbs (no venous surgery)	Ulcerated limbs (with venous surgery)
Limbs	113	119	80	39
6-month recurrence rate	47 (42)	15 (13)*	13 (16)	2 (5)
1-year recurrence rate	54 (48)	18 (15)*	16 (20)	2 (5)†

Values in parentheses are percentages. *$P<0{\cdot}01$ *versus* before ulcer clinics (χ^2 test); †$P<0{\cdot}05$ *versus* no surgery (Fisher's exact test)

A vascular-led ulcer service reduced venous ulcer recurrence. Lowest recurrence rates were seen in ulcerated limbs following venous surgery to superficial reflux. Colour venous duplex scanning is therefore essential in venous ulcer assessment.

Outcome of surgery for short saphenous vein reflux

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Short saphenous vein (SSV) surgery is more complex than that for the long saphenous vein (LSV). There is little in the literature to indicate the specific risks of the operation. A review of the outcome of SSV surgery from data collected prospectively in a single hospital is presented (1989–1996). Data were extracted from pro formas in the notes and a computerized database.

One hundred and twenty operations were performed (10 per cent of all superficial venous surgery). All surgery was performed by experienced surgeons. The vascular surgeons now undertake all SSV surgery. All patients underwent continuous wave Doppler (CWD) as outpatients; inexperienced surgeons tended to miss popliteal fossa reflux more often. Venous duplex imaging is now the norm before surgery but has increased over the years (1989–1991, none; 1992, six of 16; 1993, three of seven; 1994, 25 of 29; 1995, 39 of 44; 1996, 18 of 18).

Total morbidity was 17 per cent and the mortality rate was 2 per cent. Complications included paraesthesia (10 per cent), residual veins (4 per cent), wound infection (4 per cent), swelling (4 per cent) and deep vein thrombosis (2 per cent). There were two deaths, one from a pulmonary embolism in a patient undergoing combined LSV and SSV surgery and one from a ruptured liver in a patient on anticoagulants.

An unexpectedly high level of morbidity has been demonstrated. Patients should be aware of the risks especially in combined procedures. Duplex imaging helps to ensure that the correct procedure is undertaken, as an inexperienced operator with CWD examination may miss SSV reflux.

Systematic review of the randomized controlled trials of exercise therapy for intermittent claudication

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A systematic review was performed to determine whether exercise is an effective treatment for intermittent claudication. Two authors independently extracted details of trial quality on all randomized controlled trials of exercise *versus* control, or *versus* medical or surgical therapy in patients with intermittent claudication, and data on walking distance, measures of underlying disease and cardiovascular events. Meta-analysis was performed using the Peto method.

Nine trials were identified; five compared exercise with an untreated control group; two compared exercise with intervention (surgery and angioplasty); and two with drug regimens (antiplatelet therapy and pentoxifylline). Exercise therapy significantly improved maximal walking distance (odds ratio (OR) 6·51 (95 per cent confidence interval (c.i.) 4·36–8·66)), with an overall improvement in walking ability of 150 (range 74–230) per cent. Exercise significantly increased walking distance compared with angioplasty at 6 months (OR 2·17 (95 per cent c.i. 1·32–3·03)) and antiplatelet therapy (OR 1·06 (95 per cent c.i. 0·15–1·97)), but did not differ significantly from surgical treatment, and was less effective than pentoxifylline (OR −0·45 (95 per cent c.i. −0·66 to 0·24)). Exercise did not have a significant effect on the ankle:brachial pressure index (ABPI) or calf blood flow, and these outcomes were similar after angioplasty or antiplatelet therapy. Surgery significantly improved the ABPI (OR −0·27 (95 per cent c.i. −0·37 to −0·17)), but was associated with a higher rate of adverse events (18 per cent) and death.

Exercise is of significant benefit to patients with claudication, but further studies are required to determine the longer-term benefits of exercise compared with other successful treatments such as surgery and pentoxifylline, and to evaluate the cost effectiveness of different exercise regimens.

Total antioxidant capacity in patients with peripheral vascular disease is dependent on nutritional status rather than the severity of ischaemia

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Previous work indicates that a reduced total antioxidant capacity (TAC) increases the risk of postoperative infection in patients undergoing femorodistal bypass. It is not known whether such a reduction is dependent upon the severity of ischaemia or the patient's nutritional status. Thus the TAC and nutritional status of two groups of patients with differing severities of vascular disease was assessed (14 (nine men; median age 72 years) with critical limb ischaemia (rest pain, ankle pressure less than 50 mmHg) and 13 claudicants (seven men; median age 68 years)) and compared with that of ten controls (six men; median age 64 years). Nutritional status was assessed by mid-arm circumference, triceps skin fold thickness, body mass index, lean body mass, maximum voluntary contraction (hand grip dynamometer), bioelectrical impedance, and levels of serum albumin, prealbumin and transferrin.

Patients with peripheral vascular disease had a lower median TAC than controls (752 *versus* 1130 $\mu\text{mol l}^{-1}$, $P = 0{\cdot}05$, Mann–Whitney U test) although there was no difference between claudicants and patients with critical ischaemia (789 *versus* 721 $\mu\text{mol l}^{-1}$). However, TAC did correlate with maximum voluntary contraction ($r_s = 0{\cdot}64$, $P = 0{\cdot}037$), lean body mass ($r_s = 0{\cdot}60$, $P = 0{\cdot}043$) and serum transferrin level ($r_s = 0{\cdot}67$, $P = 0{\cdot}02$).

These results indicate that TAC is influenced by nutritional status rather than the severity of ischaemia.

Axial flow fields in a cuffed end-to-side anastomosis: effect of disease progression and angle in a simple *in vitro* model

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The addition of a distal vein cuff to a femorotibial polytetrafluoroethylene graft may improve patency but does not prevent the formation of intimal hyperplasia (IH). A flow vortex exists at the 'heel' of the cuff where shear stress is low and bloodborne factors which take part in thrombus formation or promote IH have an increased residence time. Little is known about the behaviour of this vortex with changing flow rate caused by disease progression.

A flow circuit driven by a pulsatile pump was connected to polished glass models of standard or cuffed (height 1 or 2 cm) end-to-side anastomoses (ESAs) (inflow diameter 6 mm; outflow diameters 2 mm, angles 15, 30, 45, 60°). The proximal outflow channel was occluded 2 cm from the heel. The motion of illuminated particles was captured on video and analysed frame by frame to measure the maximum vortex height. Flow rate was altered by a clamp on the inflow or outflow tubing simulating progression of disease.

	Flow rate (ml min^{-1})								
	80	100	120	80	100	120	80	100	120
	Standard ESA			1-cm cuff			2-cm cuff		
15°	44	41	42	77	77	79	121	119	122
30°	53	53	52	81	80	80	130	132	131
45°	68	66	69	95	96	96	150	148	151
60°	81	79	83	113	113	113	175	172	174

Values in the table are vortex height in pixels (median of five measurements). $P < 0{\cdot}05$ (15° *versus* 30°, 30° *versus* 45°, 45° *versus* 60°, Mann–Whitney U test)

Vortex height does not change with flow rate for a given cuff angle and ESA type, but increases with anastomotic angle ($P < 0{\cdot}05$, analysis of variance) and cuff height. The development of IH may be favoured by a tall cuff (large vortex) whereas a long and low cuff (shallow angle ESA, small vortex) may be able to better accommodate any IH before it causes a significant flow reduction. Although the smallest vortex is in a shallow standard ESA, the anastomosis volume may not be large enough to compensate for any IH that develops.

Prospective randomized trial of distal arteriovenous fistula as an adjunct to femoroinfrapopliteal bypass using polytetrafluoroethylene

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Formation of a distal arteriovenous fistula (AVF) has been advocated as an adjunct to prosthetic femoroinfrapopliteal bypass as a means of improving graft patency by augmenting blood flow above a thrombotic threshold velocity.

Over 6 years, 89 patients undergoing femoroinfrapopliteal bypass with polytetrafluoroethylene (PTFE) for critical ischaemia were randomly allocated to either AVF ($n = 48$) or control ($n = 41$). All patients had an interposition vein cuff fashioned at the distal anastomosis. Graft patency and limb salvage were assessed by means of life-table analysis.

Early trends in favour of AVF in the first 6 months were lost by 2 years. Graft patency with AVF after 6, 12, 18 and 24 months was 87, 55, 48 and 33 per cent respectively compared with 63, 43, 38 and 26 per cent for controls ($P > 0{\cdot}2$, log rank test). The limb salvage rate at 24 months in patients with an AVF was 59 per cent compared with 63 per cent in controls ($P > 0{\cdot}3$, log rank test).

The results of this prospective randomized controlled trial indicate that formation of a distal AVF confers no significant advantage in graft patency or limb salvage over interposition of a vein cuff in patients having a long, distal PTFE graft for critical ischaemia.

Infected infrainguinal grafts: the advent of methicillin-resistant *Staphylococcus aureus*

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Infected infrainguinal bypass grafts pose a major threat to life and limb. Twenty-six patients with 27 infected infrainguinal grafts treated between January 1991 and July 1997 were studied retrospectively.

The study group comprised 18 men and eight women of median age 66 (range 44–88) years. There were 17 infected femoropopliteal (16 prosthetic, one vein) and ten infected femorodistal (nine prosthetic, one vein) grafts. The median time from graft placement to infection was 3 (range 1–36) months. Eighteen patients presented with groin symptoms (sinus, false aneurysm or bleeding). Six were treated initially with local therapy (debridement, closed irrigation). Five ultimately required complete graft excision. Of these, three had a further bypass placed with limb salvage whilst two required amputation. Of the 20 patients treated initially by complete graft excision, 15 eventually required major limb amputation. Between 1991 and 1995 the infecting organisms were *Pseudomonas* and methicillin-sensitive *Staphylococcus aureus*. However, of 14 cases treated in the past 3 years all have been due to methicillin-resistant *S. aureus* (MRSA). Four patients died during the same admission from advanced sepsis. In 1991, a total of 67 infrainguinal grafts were placed and two (3 per cent) became infected. The figure for the first 8 months of this year is six (11 per cent) of 55 grafts.

Infection involving an infrainguinal bypass graft is a disastrous complication with a high amputation rate, in spite of aggressive surgery to attempt limb salvage. MRSA infection has had serious consequences, particularly in patients with prosthetic grafts.

Shared emergency vascular cover between two district general hospitals: implications for a consultant service

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A rota for weekend emergency vascular cover between four consultants from two district general hospitals was commenced on 1 February 1997. The combined catchment area includes 550 000 people with an acceptable vascular workload including 71 operations for aortic aneurysm, 34 carotid endarterectomies and over 300 angiograms/angioplasties in the 12 months preceding this study. In the first 6 months of cross-cover all vascular emergency operations were performed by consultants with no intervals left uncovered. On 14 of 25 weekends there were no vascular emergencies requiring a consultant either to be phoned or to attend the hospital. The total workload for the other 11 weekends included ten vascular operations (ranging from one to five per consultant). Emergency aortic aneurysm repair was the most common procedure (five of ten). A consultant was required to attend one of the two hospitals on nine other occasions (average less than 1 h per visit). There were 13 phone calls (160 min total) during which consultants were asked for management advice on other cases.

The advantages of consultant cover for vascular emergencies are obvious. Reservations about travelling time, increases in emergency work or two-site cover were unfounded. The amount of emergency work generated per consultant was not excessive even when added to general surgical rota duties. Based on these results the rota is being extended to include another hospital with the addition of another consultant surgeon and the rota may be widened to include weekdays.

POSSUM and P-POSSUM: is there a difference?

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Physiological and Operative Severity Score for enUmeration of Mortality and morbidity (POSSUM) has been proposed as a comparative audit tool which avoids the problems of case mix. However, it has been shown to overpredict deaths and an alternative system (P-POSSUM) was developed to overcome this problem. The methods of analysing POSSUM ('exponential') and P-POSSUM ('linear') predictions of death are different. The exponential method has not been well described and previous comparisons have therefore used the more straightforward linear analysis for POSSUM. The aim of this study was to compare the ratio of observed to expected deaths (O:E ratio) predicted by POSSUM and P-POSSUM using their correct methods of analysis in patients undergoing arterial surgery.

Some 312 consecutive patients (median age 72 (interquartile range 65–71) years; 68 per cent men) undergoing carotid endarterectomy (CEA; $n = 59$), aortic aneurysm repair (AAA; $n = 113$; 73 elective), femoropopliteal (FP; $n = 73$) or femorotibial (FT; $n = 67$) bypass, had their POSSUM and P-POSSUM scores calculated prospectively. The 30-day mortality rate was recorded using audit data, notes review and mortuary records. The O:E ratios were calculated using exponential analysis for POSSUM and linear analysis for P-POSSUM. To illustrate errors caused by using the inappropriate analysis, POSSUM and P-POSSUM were also analysed by linear and exponential analysis respectively.

There were 41 postoperative deaths (13 per cent), 25 in the AAA group (four elective); ten after FT; five after FP and one after CEA.

	POSSUM O:E ratio		P-POSSUM O:E ratio	
	Linear	Exponential	Linear	Exponential
All	0·59	0·91	1·08	0·62
CEA	0·66	1·05	0·95	0·71
AAA	0·61	1·02	0·99	0·72
FP	0·59	1·10	0·92	0·55
FT	0·70	1·00	1·01	0·68

Both POSSUM and P-POSSUM produce overall O:E ratios close to unity when the correct analysis is used. Incorrect use of linear analysis for POSSUM or exponential analysis for P-POSSUM makes each system appear to overpredict death.

Premature aortoiliac occlusive disease in young women is associated with thrombophilia

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It has been suggested that thrombophilia may be associated with the development of premature arterial occlusive disease. The aim of this study was to determine the prevalence of thrombophilia in young women with isolated aortoiliac occlusive disease (AIOD). Twenty-seven consecutive women aged under 50 years who presented with isolated AIOD and who underwent surgery or percutaneous angioplasty (with or without stent placement) were studied.

Patients had a thrombophilia screen comprising kaolin clotting time, diluted Russell viper venom time (DRVVT) with platelet neutralization, anticardiolipin immunoglobulin (Ig) G and IgM, antithrombin III activity, protein C activity, total and free protein S (immunological), activated protein C resistance activity and genetic test, and factor V (Leiden) genetic test.

One or more abnormality was detected in ten patients and comprised raised anticardiolipin IgG (five patients), raised anticardiolipin IgM (three), prolonged DRVVT not neutralized by platelets (three), prolonged kaolin clotting time (one), and low total and free protein S (one). One-third of patients with premature arterial disease in this study had detectable thrombophilia. All such patients should be screened for thrombophilia in order to identify treatable conditions.

Effect of renal artery stenting on renovascular renal failure

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Atherosclerotic renal artery stenosis is a common cause of progressive renal impairment. Percutaneous renal artery angioplasty (PTRA) may stabilize or improve renal function in 40–60 per cent of patients but may be followed by recurrence of the stenosis. It is not clear whether such patients should be considered for surgery or for stent insertion. The aim of this study was to determine the effect of insertion of a renal artery stent on the rate of progression of renal failure in patients with angiographically proven disease.

Of 428 PTRAs performed over 6 years, 20 stents were deployed in 18 patients (median age 69 (range 45–90) years) with renal impairment (median serum creatinine 252 (range 163–448) μmol l^{-1}) and haemodynamically significant native renal artery stenoses (more than 50 per cent). The indication for stent insertion was recurrent stenosis (nine of 20), ostial stenosis (eight of 20), immediate plaque recoil following PTRA (two of 20) and the presence of aneurysmal, in addition to stenotic, disease (one of 20). Stents were deployed successfully in 19 of 20 cases; one stent migrated beyond the stenosis during deployment. A false aneurysm requiring surgical intervention was the only complication. Median follow-up was 7 (range 1–34) months. In eight patients reassessed by arteriography, patency was confirmed at a median of 6 months. In 15 patients with serial serum creatinine measurement, improvement or stabilization in renal function occurred in nine.

Renal artery stent insertion has a high technical success rate and low morbidity and may benefit a significant number of patients in the short term. None the less prospective comparisons of stent deployment with surgery for renal artery stenoses are lacking.

Vascular access and the vascular surgeon: a survey of current practice

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Haemodialysis is used with increasing frequency in the elderly. The demand for vascular access surgery is met partly by vascular surgeons. The current practice and attitudes of members of the Vascular Surgical Society (VSS) towards this work has been surveyed.

Some 270 (67 per cent) of 400 members returned the questionnaire; of these 64 per cent worked in a district general hospital and 36 per cent in a teaching hospital; 67 per cent were general/vascular, 28 per cent vascular and 5 per cent vascular/transplant surgeons. Some 54 per cent of respondents provide access surgery, predominantly for renal failure. Only 6 per cent had a contractual obligation to provide such surgery and 7 per cent had an operating list specifically allocated to vascular access. Few surgeons have a heavy workload; over half performed fewer than 20 access cases per year, 20 per cent did 20–50 cases, 7 per cent 50–100 cases and 3 per cent more than 100 cases per annum.

Some 62 per cent of respondents had experienced vascular access during their training and 87 per cent felt that such surgery would be a valuable part of vascular training. Only 39 per cent of respondents' trainees are currently exposed to vascular access. Two-thirds of respondents felt that there was insufficient exposure to vascular access at British meetings with 54 per cent supporting increased exposure at the VSS.

A significant number of vascular surgeons are engaged in meeting the increasing demand for vascular access surgery. Training programmes in vascular surgery should include an adequate grounding in vascular access surgery.

Does the degree of peripheral vascular disease influence neutrophil function?

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Patients with peripheral vascular disease (PVD) have a threefold higher mortality rate compared with the general population, which is not fully explained by traditional risk factors. Leucocyte behaviour is altered in many different diseases and may be associated with an adverse clinical outcome. The aim of the study was to assess if increasing peripheral vascular ischaemia influenced neutrophil activation and degranulation.

Data were collected from 14 patients with mild/moderate claudication (ankle:brachial pressure index (ABPI) 0·8 (range 0·8–0·9)), 14 patients with severe claudication (ABPI 0·7 (range 0·6–0·8)), 25 patients with rest pain (ABPI 0·1 (range 0–0·2)) and 22 healthy age-matched controls (ABPI 1·2 (range 1·1–1·3)). Resting neutrophil count, neutrophil CD11b expression and plasma neutrophil elastase were measured. The urine albumin to creatinine ratio (UACR) was determined as a marker of systemic vascular permeability.

Patients with rest pain had significantly higher median CD11b expression ($P<0{\cdot}001$), plasma neutrophil elastase ($P<0{\cdot}05$), and urine albumin leak ($P<0{\cdot}01$) than patients with severe claudication, mild/moderate claudication and controls.

	Neutrophil CD11b (mean channel fluorescence)	Neutrophil elastase (mg l^{-1})	UACR (mg mmol^{-1})
Mild/ moderate	2·6 (2·0–3·0)	43·4 (35·3–66·3)	1·4 (0·7–2·7)†
Severe	3·5 (2·9–4·1)	44·6 (35·7–66·3)	2·3 (0·6–3·1)†
Rest pain	11·5 (7·3–15·2)*	80·3 (44·1–150·0)†	6·4 (1·0–7·5)*
Controls	2·2 (2·2–3·2)	57·4 (45·9–66·3)	0·5 (0·0–1·3)

*$P<0{\cdot}01$; †$P<0{\cdot}05$ *versus* control (Mann–Whitney U test)

This study provides evidence for the role of the neutrophil in PVD. Increasing tissue ischaemia is associated with increasing neutrophil activation and subsequent release of proteolytic enzymes with endothelial damage.

Clonality and restenosis: studies on human vascular smooth muscle cell cultures

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Restenosis after vascular intervention is largely due to vascular smooth muscle cell (VSMC) proliferation and matrix secretion. Previously, resistance to heparin-induced growth inhibition by VSMCs in culture has been linked to bypass graft restenosis *in* *vivo* in retrospective and prospective studies. Subpopulations of heparin-resistant and heparin-sensitive VSMCs probably occur in most individuals, leading to the hypothesis that the restenotic lesion may be a clonal growth of heparin-resistant cells.

VSMCs were cultured from 19 saphenous veins and six restenoses. Five to ten random subpopulations of cells from each specimen were separated in primary culture, cultured to passage two and analysed for heparin response. VSMCs were grown in 15 per cent serum with or without heparin 100 mg ml^{-1}; replenished twice weekly, and counted at 0, 7 and 14 days. Heparin inhibition was quantified as percentage inhibition comparing cell counts at day 14 in cultures with and without heparin. Some 215 (164 vein, 51 restenosis) cell subpopulations were analysed. Subpopulations derived from single samples of normal vein showed extensive variation with regard to heparin response (mean sample variation 596 per cent, corresponding to s.d. 22·6 per cent). Subpopulations derived from restenoses showed significantly less variation (mean sample variation 283 per cent, s.d. 18 per cent; $P = 0{\cdot}035$, analysis of variance, F-test). Restenosis cell subpopulations were confirmed to be more heparin resistant than normal vein cells (12·7 *versus* 37·3 per cent inhibition; $P = 0{\cdot}00002$, *t*-test). Random subpopulations derived from vein showed diversity; random subpopulations from restenosis showed relative uniformity.

These data support the concept that polyclonal subpopulations of VSMCs exist in normal veins, and that restenotic lesions represent an oligoclonal selection of heparin-resistant subpopulations.

Increased expression of metalloproteinase 2 in aneurysm-derived smooth muscle cells: the primary event in aneurysm formation?

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Histopathological and biochemical studies of abdominal aortic aneurysms (AAAs) have demonstrated widespread elastin degradation, which has been attributed to increased levels of proteolytic metalloproteinases (MMPs) within the arterial tissue. Unfortunately, these historical studies have used established aneurysm tissue which makes primary aetiological changes impossible to differentiate from secondary degenerative effects. To overcome these problems, the present study has characterized the properties of isolated vascular smooth muscle cells (SMCs) cultured from the aortic wall of patients with either aneurysm or occlusive disease.

Sixteen individual SMC cell lines have been established from the aortic walls of aneurysm ($n = 9$) or atherosclerotic ($n = 7$) specimens. There was no difference in the proliferation rate between the two cellular groups. The production of MMP-2 and -9, in addition to that of their inhibitors TIMP-2 and TIMP-1, was quantified by direct assay (ng protein per 10^5 cells) and substrate gel enzymography (OD).

Cell line	MMP-2 (zymogram)	MMP-2 (ELISA)	MMP-9	TIMP-1	TIMP-2
AAA	2·6 (1·5–8·2)	361 (148–750)	1·2 (0·8–1·6)	677 (354–1014)	49 (29–90)
Athero-sclerotic	2·1 (1·6–6·4)*	324 (250–452)*	0·7 (0·6–0·8)	613 (363–3349)	8 (0–23)

Values are median (range). ELISA, enzyme-linked immunosorbent assay. *$P < 0{\cdot}05$ *versus* AAA (non-parametric analysis)

These results demonstrated an increased production of MMP-2 in aneurysm-derived SMCs. Quantification of patients' serum revealed no difference between the groups, neither did stimulation by interleukin 1β. However, analysis of MMP-2 gene expression by Northern blotting and reverse transcriptase–polymerase chain reaction demonstrated a primary overexpression of MMP-2 in aneurysm-derived cells.

The development of AAAs could be attributed to a single genetic locus. Data from this study suggest a primary enhancement of MMP-2 expression and production in aneurysm cells; MMP-2 may be a strong candidate gene for aneurysm development.

Vascular Surgical Society audit of acute lower limb ischaemia: outcomes of treatment and results of a validation exercise

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Initial figures from a 3-month audit of 539 cases of acute lower limb ischaemia have already been presented, and outcomes of treatment have now been analysed. At 30 days (or death/discharge) 70 per cent of limbs were definitely viable, 21 per cent after no vascular intervention, 59 per cent after anticoagulation only, 73 per cent after immediate embolectomy and 73 per cent overall after arteriography (74 per cent following subsequent thrombolysis and 81 per cent after bypass grafting). However, amputation rates (15 per cent overall) were similar for all types of treatment, ranging from 11 per cent after an arteriogram followed by embolectomy to 17 per cent after no vascular intervention (*P* not significant). Patients having no intervention were significantly older (median 83 years) than the cohort as a whole (median 73 years) ($P < 0{\cdot}001$). The overall mortality rate was 22 per cent.

These patients had been reported by 86 of 182 hospitals asked to participate, with substantial differences between regions (response rate 0–82 per cent). A validation exercise of 54 cases (10 per cent sample) from five non-participating hospitals showed no significant difference in age (median 73 *versus* 77 years in the 10 per cent sample), admitting specialty (55 *versus* 62 per cent vascular), or vascular advice (95 per cent in both). In each group 24 per cent had no intervention or anticoagulants, 21 *versus* 15 per cent embolectomy (*P* not significant), and 55 *versus* 43 per cent initial arteriograms (*P* not significant). At 30 days 64 per cent of limbs were viable and 20 per cent of patients had died in the validation sample (*P* not significant).

Small numbers of cases, diversity of treatments and selective use of different management strategies made direct comparisons between individual hospitals unrealistic. There was a variety of reasons for hospitals not contributing, but a 10 per cent validation sample showed no substantial differences from the original audit.

Criteria for arteriography following duplex evaluation of peripheral arterial disease

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Arterial reconstruction of the lower limb based on duplex imaging is controversial. This study assessed duplex accuracy and determined the conditions for which arteriography is mandatory following duplex imaging.

Some 156 patients (97 men, 54 women; mean age 68 years) were divided into two groups. Ninety patients (group 1) had duplex imaging and arteriography of the lower limb. Duplex accuracy was compared with arteriography (gold standard). Some 66 patients (group 2) had duplex imaging as the main investigation. Treatment was based on duplex findings. Arteriography was done on request of the surgeon. Duplex accuracy was also obtained for this group. The results of both groups were analysed and criteria for arteriography were obtained.

Some 3108 arterial segments (group 1) were examined in 177 limbs by both modalities; 466 arterial lesions were detected. Disagreement between duplex imaging and arteriography was found in 71 lesions. Duplex imaging had a sensitivity of 92 per cent, specificity 99 per cent, positive predictive value 91 per cent and negative predictive value 100 per cent with kappa of 0·87(0·06). Some 2310 arterial segments (group 2) were examined in 122 limbs by duplex imaging. Treatment decisions are shown in the *Table*. The criteria for arteriography following duplex were 1, failure of scanning to visualize an artery of interest; 2, failure of sonographer to comment on the profunda femoris, if considered important in clinical management; 3, difficult scanning of distal femoral and popliteal arteries; and 4, femorodistal bypass graft considered necessary.

Treatment	No. of patients	Percentage having arteriography
Discharge	8 (12)	0
Conservative	25 (38)	0
Balloon angioplasty	21 (32)	0
Surgery	3 (5)	67
Arteriography	9 (14)	100

Values in parentheses are percentages

Duplex imaging can be used safely for assessment of peripheral arterial disease and angioplasty can be planned without the need for diagnostic arteriography.

Variability of angiographic measurements of internal carotid artery stenosis between methods and observers

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Accurate measurement of carotid artery stenosis is an essential prerequisite for evidence-based carotid endarterectomy. Only the minority of patients in whom carotid duplex sonography is non-diagnostic now have carotid angiography. The aim of this study was to determine in this selected group the intraobserver and interobserver variability in the measurement of percentage stenosis.

Measurements were made in each case on the angiogram showing the greatest stenosis by 'eyeballing', calipers and a ruler, and jeweller's (Schindler scale) eyepiece graduated in fifths of a millimetre. Three independent observers were blinded to the measurements for each technique and to each other's results. One observer repeated all observations after 2 weeks to assess intraobserver error. Data were analysed using analysis of variance and the degree of correlation.

The three observers measured 90 stenoses by each of the three techniques. The correlation coefficients are tabulated.

Correlation	NASCET	ECST	Common carotid (CC) denominator
Intraobserver error			
Ruler	0·78	0·81	0·79
Scale	0·90	0·87	0·94
Intraobserver error 1			
Ruler	0·82	0·94	0·92
Scale	0·84	0·85	0·86
Eyeball	0·59	0·54	
Intraobserver error 2			
Ruler	0·82	0·44	0·80
Scale	0·80	0·84	0·87
Eyeball	0·74	0·73	

NASCET, North American Symptomatic Carotid Endarterectomy Trial; ECST, European Carotid Surgery Trial

The number of stenoses within each group measured by the ECST and CC denominator methods was similar, but NASCET classified 16 per cent more stenoses as mild (less than 30 per cent). NASCET also classified 50 per cent of severe stenoses according to ECST into the moderate group (30–69 per cent). There were poor correlations for interobserver and intraobserver measurements, and between methods of assigning category of stenosis.

The differences among observers and techniques for measuring angiographic carotid artery stenoses are considerable. These measurement discrepancies compound the known differences in percentage stenosis calculated by NASCET, ECST and CC denominator methods.

Fast gadolinium-enhanced magnetic resonance angiography: a technique to replace digital subtraction angiography?

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Digital subtraction angiography (DSA) is an invasive procedure with small but finite risks (vascular trauma, contrast reaction, radiation). Magnetic resonance angiography (MRA) avoids these problems although standard time-of-flight imaging is slow and may not differentiate between tight stenoses and occlusions. A novel technique of MRA (gadolinium-enhanced contrast imaging; MRA-G) and a 'floating' table, as used for angiography, has been developed.

Twenty patients (ten with intermittent claudication, ten with critical ischaemia; 14 men and six women) underwent DSA and MRA-G. Gadolinium (40 ml, 0·1 mmol l^{-1}) was delivered via a peripheral vein over 2 min and imaging performed on a state of the art 1·5-T magnet. MRA images were acquired in 90 s over the abdomen/pelvis, thighs and legs (30 s each) providing images from the diaphragm to the foot. Reformatting allowed multiplanar views of all segments after a single contrast injection and scan.

All MRA-G studies were technically successful. Both the MRA-G and DSA films were assessed by two radiologists and two vascular surgeons. All occlusions/stenoses demonstrated by DSA were apparent on MRA-G. Furthermore patent crural vessels were detected by MRA-G in four patients when not evident on DSA. In all patients the therapeutic decision based on MRA-G was identical to that for DSA.

MRA-G may have a primary role for the rapid, non-invasive evaluation of patients with peripheral vascular disease providing images of comparable quality to DSA but with additional advantages of multiplanar views in all segments, routine demonstration of the whole of the intra-abdominal aorta and its branches, and enhanced imaging of crural vessels.

Percutaneous stent grafting of superficial femoral artery disease: 1-year follow-up of a pilot study

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Endovascular treatment has been proposed as an alternative to angioplasty or surgical bypass in patients with disabling claudication who have superficial femoral artery (SFA) occlusion. A pilot study was carried out to evaluate a balloon-mounted stent graft system made of polytetrafluoroethylene with proximal and distal anchoring stents.

After ethics committee approval, 20 patients with severe claudication (median age 64 (range 48–76) years; 19 men) were treated. All had SFA occlusions (median length 17 (interquartile range 10–20) cm) and satisfied the entry criteria (two or more run-off vessels; minimum SFA diameter at stent anchor sites 4 mm; proximal and distal disease-free anchor sites). Procedures were performed under local (seven patients), general (12) or epidural (two) anaesthesia using a 9-Fr introducer sheath, intravascular ultrasonography (IVUS) and image intensifier.

Vessel dissection by the introducer sheath accounted for two technical failures. Four other procedures were abandoned because IVUS measurements were outside protocol requirements. Of the 14 stents deployed, five occluded in the first month. Collapse of the unsupported section was the cause in two. The other three patients declined further intervention. Of the nine stent grafts patent at 1 year, only three are patent without intervention; one had angioplasty of an inflow stenosis and five developed significant intimal hyperplasia in the stented sections, requiring angioplasty with or without atherectomy. The 1-year primary, primary-assisted and secondary patency rates were 13, 24 and 36 per cent respectively (standard error 6, 10 and 11 per cent respectively). There were no deaths.

Preliminary results using this device are discouraging. If stent grafting of SFA disease is to become a viable alternative to surgery, fully supported designs which resist compression may be necessary, and the problems of intimal hyperplasia will have to be overcome.

Quality control during endovascular aneurysm repair

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With endovascular aneurysm repair there remains the potential for complications associated with graft deployment which would not occur during conventional surgery. If the technique is to achieve widespread acceptance it is essential to minimize such complications. The aim of this study was to employ direct measurement of aneurysm sac pressure and Doppler flow monitoring of the superficial femoral artery (SFA) to ensure complete exclusion of the aneurysm from the circulation.

An angiographic catheter was passed via an iliac conduit into the aneurysm sac of ten consecutive patients undergoing endovascular aortouniiliac repair. This was connected to an external pressure transducer allowing pressure monitoring during and for 24 h after the procedure. Flow was monitored in the SFA by insonation with a 2-MHz Doppler ultrasound probe. No technical defect was found in the deployment of seven of ten stents. Aneurysm sac pressure as a percentage of systolic blood pressure is shown in the *Table*.

	Predeployment	Postdeployment	Completion	24 h after operation
Aneurysm pressure (% systolic pressure)	109 (95–121)	59 (38–86)	41 (34–75)	52 (27–73)

Values are median (range)

In three cases technical problems were detected. In two patients the aneurysm sac pressure rose towards completion. Poor SFA flow was detected in one and contrast injected into the aneurysm sac revealed incomplete iliac occlusion, requiring open ligation. The second had good SFA flow and contrast injection revealed large patent lumbar vessels. Contrast injection at 24 h revealed complete exclusion of the sac. In a further patient incomplete stent deployment was detected by a rise in sac pressure to systolic pressure after balloon deflation.

Monitoring aneurysm pressure in combination with SFA Doppler flow can detect complications of endovascular aneurysm repair which can be corrected at operation.

Longitudinal aneurysm shrinkage following endovascular aortic aneurysm repair is a source of intermediate and late complications

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Successful endovascular aortic aneurysm repair results in thrombosis and shrinking of the sac, observed as a reduction in maximum transverse diameter (known as D3) with serial scanning. There are, however, no published data relating to alterations in the longitudinal parameter from renal arteries to aortic bifurcation (known as H3).

Patients undergoing endovascular aortic aneurysm repair were followed up by the EUROSTAR protocol, with regular computed tomography and angiography. Minimum 3-month follow-up (median 12 (range 3–18) months) has been completed in 25 patients. Aneurysm morphology was analysed according to serial changes in H3 and D3, with changes of more than 5 mm and greater than 2 mm respectively being considered significant.

Reduction in H3 was observed in 17 patients, of whom eight had a concurrent fall in D3. Reduction in D3 alone was only seen once. Progressive kinking of the stent graft was seen in seven patients, all with combined reduction in H3 and D3, and was associated with dislocation of the stump of a bifurcated system in two. In the eight patients with H3 reduction alone there was one distal endoleak and one iliac limb thrombosis. The four complications were salvaged by secondary endovascular means (three) and surgery (one).

Following endovascular aortic aneurysm repair, D3 reduction occurs less commonly than H3 reduction, and is not necessarily a favourable observation. The previously unreported phenomenon of longitudinal shrinkage (H3 reduction), both in isolation and in combination with transverse shrinkage (D3 reduction), was associated with a significant complication rate.

Significance of endoleaks after endovascular aneurysm repair

G. L. Gilling-Smith, on behalf of the EUROSTAR collaborators

The presence of an endoleak after endovascular repair of an abdominal aortic aneurysm (AAA) may be considered to represent failure of treatment since it signifies persistent or new communication between the circulation and the aneurysm sac. However, the relationship between endoleak, continued aneurysm expansion and late aneurysm rupture remains unknown.

Between May 1994 and June 1997, endovascular repair of AAA was attempted in 430 patients. Ten patients required conversion to open operation and a further 12 died within 30 days. The remaining 408 patients were followed for a median of 10 (range 1–36) months. The presence or absence of endoleaks and changes in the maximum transverse diameter of the aneurysm (MTD) were determined by serial contrast-enhanced computed tomography (CT) at 1, 3, 6, 12, 18 and 24 months after operation.

Endoleaks were observed on completion angiography and/or predischarge CT in 66 patients (16 per cent). A further 27 patients developed endoleaks during follow-up. Twenty-four leaks closed spontaneously, 27 were treated by additional endovascular intervention and three by open operation. One late rupture following development of a midgraft leak was successfully treated by open operation. Overall there was a progressive reduction in MTD during follow-up. However, an increase in MTD was observed in more than 20 per cent of patients at 12 months and this occurred significantly more frequently in patients with endoleaks (*Table*).

	No endoleak ($n = 141$)	Endoleak ($n = 42$)
MTD increasing*	11	53†
MTD decreasing*	73	40†
No change in MTD*	16	7†
Mean (s.d.) change in MTD (mm)	−5·1(7·2)	2·1(10·7)

*Values are percentage of patients; changes in MTD 12 months after endovascular repair of AAA; †$P < 0{\cdot}01$ (χ^2 test)

Continued expansion of the aneurysm is more likely in patients with endoleaks but infrequently leads to aneurysm rupture within a year of surgery. Further follow-up is required to evaluate the long-term fate of these aneurysms and to determine if the natural history is influenced by secondary closure of endoleaks.

Management of patients with failed endovascular stents

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Percutaneous transluminal angioplasty (PTA) with endovascular stenting is now commonly used in the treatment of aortoiliac occlusive disease. There are limited data on the long-term outcome of patients in whom stenting fails. A retrospective analysis of all patients who underwent stenting in whom the treatment failed has been carried out.

Between July 1993 and July 1996, a total of 80 patients had iliac stents inserted. In 19 patients the stent failed. There were 14 women and five men with a mean age of 55 (range 35–92) years. Fifteen presented with intermittent claudication and four with rest pain. All patients had aortoiliac occlusive disease which on arteriography was suitable for PTA. Six patients had Palmaz 294 stents, seven patients had kissing Palmaz 394 stents and six had wall stents. In eight patients the stent blocked immediately; radiological salvage was possible in four with good symptomatic outcome. In the other four patients, arterial reconstruction surgery was performed. Only one patient had a successful outcome and three eventually required amputation of the lower limb. In 11 patients the stents blocked at between 1 month and 4 years. In two, radiological salvage was attempted but failed and arterial bypass surgery was performed which was successful in one. Of the remaining nine patients who underwent arterial reconstructive surgery, six remain symptom free and three still have claudication.

Although stenting of iliac disease is widespread, experience suggests that complications are not uncommon. Surgery rather than further radiological intervention is usually needed.

Registry of Endovascular Treatment of Aneurysms: first year's results

S. Thomas, *on behalf of the Joint Working Party of the Vascular Surgical Society of Great Britain and Ireland*

The feasibility of endovascular repair of abdominal aortic aneurysms has been proven. Until the safety and efficacy of the technique has been established, its introduction into clinical practice needs to be carefully evaluated.

The Registry of Endovascular Treatment of Aneurysms (RETA) is based on a simple form which is machine readable. Between January and December 1996, a total of 139 forms were received from the 12 centres in the UK performing this technique. A median of nine (range 1–32) procedures were performed per centre and all involved a vascular surgeon and an interventional radiologist. Twelve aortic tube devices, 63 aortobiiliac devices and 64 aortouniiliac devices with additional crossover grafts were used. Forty-eight patients were considered unfit for conventional surgery.

At the end of the initial procedure 101 aneurysms (73 per cent) were successfully excluded with no complications. Ten patients required conversion to open repair and 21 required additional endovascular or surgical procedures. At 30 days, 118 aneurysms (85 per cent) were excluded or had been repaired. There were eight persistent leaks (6 per cent), one amputation and 13 deaths (9 per cent). The death rate was related to the fitness of the patient (7 per cent fit and 15 per cent unfit), type of device (4 per cent for tube or bifurcation devices *versus* 15 per cent for aortouniiliac and crossover) and need for conversion (50 per cent).

The preliminary results of the Registry support the need for continued evaluation, especially in the longer term. The short-term results support the proposal for a randomized trial of endovascular *versus* conventional repair in fit patients and endovascular repair *versus* conservative treatment in unfit patients. The appropriateness of conversion following failed endovascular repair needs careful consideration in unfit patients.

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Popliteal vein reflux reduces the healing of chronic venous ulcer

Sir

I enjoyed the article by Brittenden *et al.* (*Br J Surg* 1998; **85**: 60–2) in which there was reference to work from our department regarding management of patients with venous ulceration with saphenous and perforator incompetence alone[1]. These patients were healed by ligation of the incompetent saphenous system. No perforator ligation was performed as incorrectly stated by the authors. I think this is an important distinction.

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Predicting changes in the distribution of sweating following thoracoscopic sympathectomy

Sir

Andrews and Rennie (*Br J Surg* 1997; **84**: 1702–4) reiterate the myth that, in the treatment of palmar hyperhidrosis, it is necessary 'to divide, or ablate with diathermy, the second, third and possibly the fourth thoracic sympathetic ganglia'. The sympathetic nerves supplying the upper limb arise from the second to the sixth spinal thoracic segments. They join the sympathetic trunk after either synapsing in, or passing through, the segmental thoracic ganglia. They reach the upper limb by joining somatic nerves arising from the fifth cervical to the first thoracic spinal segments, i.e. the brachial plexus. It follows that they are present in the sympathetic trunk between the first and second thoracic ganglia. Division of the sympathetic trunk on the second rib will interrupt all sympathetic outflow to the hand except that which might pass through the nerves of Kuntz or the intercostobrachial nerve.

It has always been my practise to treat palmar hyperhidrosis by division of the sympathetic trunk on the second rib with scissors. To date, the operation has never failed to produce an immediate cure. By restricting the use of diathermy to the inferior end of the divided sympathetic trunk no patient need experience the unnecessary complications of ptosis or miosis.

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Author's reply

Sir

I am grateful to Mr Collin for his response to our paper and agree that to achieve dryness of the hand a T2 sympathectomy alone, either by diathermy ablation or scissor dissection, is adequate. It had been our practice previously to perform a T2–3 sympathectomy, but we are now of the opinion that a T2 sympathectomy alone is adequate.

The reason we had previously been performing T2–4 sympathectomies was to achieve a simultaneous dryness of the axilla as well as the hand. We have found consistently that a T2–4 sympathectomy achieves about 80 per cent dryness of the axilla as well as the inevitable complete dryness of the hand.

However, as stressed in our paper, the risk of performing a more extensive, i.e. T2–4 sympathectomy, is the higher incidence of compensatory sweating, and we now recommend a T2–3 sympathectomy alone for hyperhidrosis of the hand and axilla.

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Hereditary breast cancer

Sir

We read with interest the recent Review (*Br J Surg* 1997; **84**: 1334–9) on hereditary breast cancer, but feel that an important area was neglected, namely the management of patients with breast cancer in whom a mutation in the *BRCA1* or *BRCA2* gene has been identified. Hill *et al.* report the risk of breast cancer to be as high as 87 per cent by the age of 70 years in women with the *BRCA1* mutation, and up to 87 per cent by the age of 80 years with the *BRCA2* mutation. Breast surgeons will undoubtedly be referred an ever-increasing number of women with breast cancer who are either known or are subsequently found to carry such a gene mutation. It has also been reported recently that breast carcinoma in these patients is of a differernt histological type and higher grade than that in controls[1]. Should these patients be treated differently? Do they have a higher chance of local recurrence following conservation, and do they have a higher rate of contralateral breast cancer? The answers to these questions are presently unknown.

The lifetime risk of subsequent ovarian cancer in such patients is said to be 50–60 per cent (references 16 and 30 in article). Ovarian ablation as adjuvant therapy for breast cancer in premenopausal women has been shown to have similar efficacy to chemotherapy in terms of both event-free and overall survival[2]. A survival benefit has been demonstrated for ovarian ablation plus adjuvant chemotherapy rather than adjuvant chemotherapy alone for oestrogen receptor positive tumours[3].

A logical approach to adjuvant therapy in patients with *BRCA1* or *BRCA2* associated breast cancer would be to employ laparoscopic oophorectomy which could, at the same time, potentially reduce the risk of subsequent ovarian cancer.

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1 Breast Cancer Linkage Consortium. Pathology of familial breast cancer: differences between breast cancers in carriers of *BRCA1* or *BRCA2* mutations and sporadic cases. *Lancet* 1997; **349**: 1505–10.

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Laparoscopy for the impalpable testis

Sir

Godbole *et al.* (*Br J Surg* 1997; **84**: 1430–2) record the continuing use of the inguinal canal as a recognized route for the exploration of an impalpable testis and reference three recent papers in which this route had been used in 43 boys, with a negative result, before referral to a paediatric unit. We must now hope that the advice of all these authors to regard this practice as 'unjustified' will be generally accepted.

Since the work of La Roque[1] in 1931 demonstrated its defects, it has been general experience that exploration for an impalpable testis through the inguinal canal is frequently unsatisfactory; this is because access to the intra-abdominal testis and the tethered retroperitoneal testicular vessels is so restricted. Frustration with this poor access and experience with Henry's approach to the femoral hernia led (in prelaparoscopy days) to the use of a preperitoneal approach. Using a Weir muscle-splitting incision gave excellent access to a testis some distance above the internal abdominal ring and made it easy to mobilize apparently short testicular vessels[2].

The authors and others have shown how helpful laparoscopy can be in selecting patients for whom exploration is useful and it is then well worthwhile to consider use of the preperitoneal approach. We note that they achieved 'standard' orchidopexy in 25 of 32 boys with an intra-abdominal testis and only used the Fowler–Stephens procedure on six occasions. In view of the difficulties that attend orchidopexy for these testes, it would be interesting to know the route used in the 25 orchidopexies and the long-term results.

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Helicobacter pylori and peptic ulcer surgery

Sir

I read with interest the views of Chung and Li (*Br J Surg* 1997; **84**: 1491–2) on the impact of *Helicobacter pylori* on peptic ulcer disease. In particular, it was useful to contrast the implications for surgery between the clear efficacy of *H. pylori* eradication as secondary prevention for ulcer haemorrhage and the balanced caution expressed regarding the long-term outlook for anti-*H. pylori* and endoscopic therapies for gastric outlet obstruction.

On currently available evidence, however, the authors may have overstated the case by implicating *H. pylori* in the causation of perforated ulcers and in their conclusions concerning the effect of *H. pylori* eradication on perforated ulcers. Until more definitive studies are performed, the aetiological role of *H. pylori* in perforated ulcer will remain controversial. The only adequately controlled study demonstrated no increase in prevalence of *H. pylori* infection (47 per cent of perforated ulcers *versus* 50 per cent of controls)[1]. Two other studies have demonstrated slightly higher rates of 24 of 29[2] and 51 of 73[3], but without including control groups. In contrast to the situation in ulcer bleeding[4], there are no trials (randomized or otherwise) illustrating that *H. pylori* eradication alters the natural history of ulcer perforation. While it seems reasonable to give anti-*H. pylori* therapy to those with infection, it is essential to recognize that the recommended approach of patch repair and antibiotics is not yet supported by trial data. Recurrent ulceration and perforation occurs after simple patch repair even if pharmacological acid suppression is continued[5,6]. In the author's own series 16 per cent of patients had no easily reversible risk factor (*H. pylori* or non-steroidal anti-inflammatory drugs) showing that *H. pylori* eradication will not affect this substantial subgroup[3].

Well conducted trials have now been performed in the management of patients with bleeding ulcers[4], and it would be appropriate for similar studies to define the roles of surgery, *H. pylori* eradication and pharmacological acid suppression in the treatment of perforated ulcer.

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Early effect of carotid endarterectomy on arterial blood pressure measured with an ambulatory monitor

Sir

We were interested to read the article by Dodds *et al.* (*Br J Surg* 1997; **84**: 1104–6) on the effects of carotid endarterectomy on arterial blood pressure 2 weeks after surgery but disappointed they did not provide more information about the surgical techniques used.

They suggested that the fall in blood pressure following carotid endarterectomy was a result of increased firing of the carotid sinus baroreceptors, as in the postoperative period there would be an increased lateral pressure on the carotid sinus wall (loss of Venturi effect) and an increased radius, thereby increasing sinus wall tension (Law of Laplace, T = PR). The diameter of the carotid sinus often increases after endarterectomy without patching[1], and Eastcott[2] postulated that the use of a patch in closure would widen the sinus even further, thereby creating a more dramatic reduction in blood pressure. The type of material used may also be of relevance in affecting compliance. It is therefore important to know whether patching was used for the ten patients in this study. They also mention that they preserved the carotid sinus nerve 'where possible' and it would be useful to know how often this was not possible and if these patients also showed a fall in blood pressure after 2 weeks. Finally, we wonder whether there are long-term results to compare their results with previous studies, which found no long-term alteration in blood pressure[3].

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Author's reply

Sir

The haemodynamic and biomechanical effects of carotid endarterectomy on carotid sinus function and blood pressure regulation are the result of a complex interaction between at least three factors: the loss of the pressure gradient across the stenosis, the mechanical effect of a patch angioplasty, and possible operative damage to the carotid sinus nerve. Two methods are commonly used to measure the effect of surgery: (1) measurement of carotid sinus sensitivity such as change in heart-rate in response to reduced neck pressure or altered arterial pressure; and (2) measurement of blood pressure. In their studies Angell-James and Lumley[1], and Dehn and Angell-James[2] both measured carotid sinus sensitivity and both showed three types of response after surgery with an inverse relationship between carotid sinus nerve function and blood pressure. However, such studies are difficult to repeat in groups of patients large enough to allow the effect of individual factors to be analysed over a long follow-up interval. The alternative option is blood pressure management, which is itself complicated by the variability of blood pressure, and the problems this introduces for single measurements. Our primary finding was that, if ambulatory blood pressure measurement is used, the effect of blood pressure variability is reduced and only small groups of patients are required to show a significant change in the mean blood pressure. The study was not powered to show the separate effects of stenosis severity, patching or nerve preservation, and so to avoid a type II error the data on which patients were patched were not presented. In considering the mechanical effect of endarterectomy the stress–strain relationship for arteries is non-linear, and in fact shows an increase in stiffness with strain. It is therefore expected that increased arterial diameter secondary to increased pressure or a patch angioplasty will result in reduced compliance[1]. The effect on carotid sinus function is not so predictable as it depends on whether the carotid sinus measures dynamic or static strain[3], and the degree of long-term adaptation. While a nerve-preserving dissection was employed, we did not measure carotid sinus sensitivity and so cannot comment on which patients suffered nerve damage. As with previous studies, however, we did observe some patients who had only a small fall in blood pressure, and others in whom it was much more marked. Finally, the evidence in the literature about the long-term effect of carotid endarterectomy requires careful interpretation. Dehn and Angell-James[2] showed no change in mean blood pressure for the whole group at 6 months but there was a measurable long-term effect on carotid sinus sensitivity for individual patients. Further evidence for there being two separate groups of patients is given by Hirschl *et al.*[4], who showed that for longer follow-up, an increase in carotid sinus sensitivity is associated with reduced blood pressure, while a decrease in carotid sinus sensitivity was associated with increased incidence of major vascular events.

We accept the validity of the points raised but recommend that a larger study employing measurements of both carotid sinus sensitivity and ambulatory blood pressure is required. Such a study would appear to be worthwhile if, for some patients at least, carotid endarterectomy is associated with a long-term reduction in the risk of a major vascular event.

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Book reviews

Video-Book. Per Urethral Endourological Operative Techniques (For Rigid Endoscopies Only)

S. S. Bapat (ed.). 250 × 225 mm. Pp. 325. Two videotapes (408 min). Illustrated. 1996. Tuttlingen: Karl Storz. Price not supplied.

Professor Bapat has put a great deal of work into producing this video book. As indicated in the title, the book does not cover the entire field of endourology; there is no chapter on percutaneous nephrolithotomy. The book is also restricted to endourological techniques with rigid instruments; flexible cystoscopy and flexible ureteroscopy are not covered. It is directed towards the urological higher surgical trainee and would be of most benefit to a trainee starting his/her urology career. The chapters are written to coincide with the video; this is the concept of the video book. In this respect, the work is virtually unique. Its strength lies in the enormous amount of clinical material covered in the video section. All common endourological procedures, other than percutaneous nephrolithotomy, are covered and the reader is able to familiarize him or herself with standard endoscopic procedures. The endoscopic features of a wide range of urological conditions have been captured on video. The weaknesses are in the quality of the sound and, in places, the picture. The video is on two cassettes with a viewing time of 408 min, which is probably too long. The continuous background music can become tedious, but the chapters on transurethral prostatectomy and ureteroscopy are particularly good. Despite the rather amateur quality, there is a great deal of interesting clinical material presented, but it is of limited appeal to the practising urologist with experience in endourological techniques. There are likely to be more publications of this type to help demonstrate endourological procedures to the urological trainee and to familiarize practising urologists with new techniques.

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Case Presentations for the MRCS and AFRCS (three volumes)

P. Hornick, J. S. P. Lumley, P. A. Grace (eds). 209 × 130 mm. Pp. 199 pp (vol. 1); 188 pp (vol. 2); 191 pp (vol. 3). Illustrated. 1997. Oxford: Butterworth-Heinemann. £14.99 per volume.

This three-volume book contains 111 case presentations intended for candidates for the MRCS and AFRCS examinations. Each case history is followed by up to ten questions which are then answered at an appropriate level by contributors, many of whom are national authorities in their field. The range of subjects chosen corresponds with the MRCS/AFRCS syllabus.

Is there a need for such a book? Although I was initially sceptical, after reviewing the volumes I am more convinced that this work will be a useful addition to the reading material for basic surgical trainees. The case presentations could be used in a number of ways. For instance, after reading the standard texts, candidates may find it useful to put their knowledge to the test by reading the case histories and then attempting to answer the questions. A comparison may then be made between their own answer and the book answer. The book will also come in handy for last-minute revision and, in addition, it provides insight into the level of knowledge required for examination. In this context I suggest that the 'height of the hurdle' set by the contributor in a few of the answers is a little higher than I would expect for the MRCS and AFRCS examinations. This is a small criticism. The editors and contributors should be congratulated on producing such a valuable book and I have already recommended it to senior house officers preparing for the examination. I would suggest tentatively that examiners for the MRCS and AFRCS examinations might also find it interesting to browse through.

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Tropical Surgery – A Vademecum Series Book

R. V. Cohen and F. Aun (eds). 215 × 141 mm. Pp. 337. Illustrated. 1997. Basel: Karger Landes Systems. US$49.

It is difficult to find such an interesting book about the main surgical diseases of the tropical and subtropical areas of the world, although millions of inhabitants of those areas are still suffering from the diseases. After reviewing this handbook of *Tropical Surgery*, I have to accept that this is one of a limited number of very high standard books. Each chapter is generally well written with excellent figures, and covers important and relevant information. The format of this handbook allows readers to spend only a short period of time in understanding clinical features, how to make a diagnosis and how to grasp the principles of surgical management. The content is up to date and the examples of imaging studies are very clear. Moreover, at the end of each chapter, the authors provide a list of suggested reading with a short commentary. I consider this book to be splendid and that not only a surgeon, but also a general practitioner or even a physician, would benefit from reading it.

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Atlas of Surgical Technique in Urology

E. D. Whitehead (ed.). 310 × 235 mm. Pp. 578. Illustrated. 1997. Philadelphia, Pennsylvania: Lippincott-Raven. £134.25.

This volume, with an exclusively North American authorship, is presented as an illustrated textbook of operations. The aim of the editor was to produce an atlas of operations based on well written operative reports and accompanying illustrations. This has resulted in a somewhat diverse style of writing and considerable variability in the detail of each operative description. The atlas certainly allows the urologist to 'participate in the operation described', but some of the chapters do not always provide sufficient detail to enable the urologist, who has perhaps only seen the procedure once or twice, to read up on the operation and then perform it. One or two of the illustrations are a little eccentric and superfluous, but for the most part they are of good quality. There are one or two surprising omissions which perhaps reflect North American practice (for example, removal of a staghorn calculus by extended phyelolithotomy and radial nephrotomies), and one or two surprising inclusions (open pyelolithotomy, anatrophic nephrolithotomy and balloon dilatation of the prostate). It is surprising that there is no mention of endoscopic techniques for ureteropelvic junction obstruction; the only description of open surgery for ureteropelvic junction obstruction is that of a Hynes Anderson pyeloplasty without any clear attribution to the original authors in the description of the procedure. For me, the book does not quite succeed in achieving its objectives. It is a welcome addition to my own library, but the acid test is 'would I buy it for the department?' The answer to this question has to be 'no' as there are competing texts which are of more value to the UK urologist.

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Endosurgery (CD-ROM)

J. Toouli, D. Gossot and J. G. Hunter (eds). Illustrated.
1997. New York: Churchill Livingstone. £185.

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Leading articles

Cystic tumours of the pancreas

Cystic tumours of the pancreas comprise neoplasms of epithelial and other origin and congenital pseudotumours. Epithelial tumours make up 90 per cent of cystic tumours of the pancreas[1]. Recently these tumours have been classified with a system that defines each tumour with a single name and a precise histological grade[2]. The commonest epithelial tumours are benign cystadenomas (serous or mucinous) and cystadenocarcinomas, which together represent three quarters of all these cystic tumours[1,3].

After discovery of a cystic lesion in the pancreatic region there are three necessary diagnostic steps: (1) to confirm the intrapancreatic origin of the cyst, (2) to rule out the diagnosis of pseudocyst and (3) to identify those cystic tumours which should be resected because of actual or potential malignancy. The clinical context and the history can be conclusive in this sequence. Ultrasonography is valuable for detection of cystic lesions. Spiral computed tomography (CT) with intravenous contrast enhancement is the examination of choice and is usually sufficient for anatomical localization and diagnosis in the majority of cystic tumours. Arteriography does not contribute to diagnosis and occasionally study of cyst fluid, endoscopic ultrasonography, retrograde pancreatography or magnetic resonance pancreatography, and endoscopic pancreatoscopy may be helpful.

Serous cystadenomas are the commonest single type of cystic tumour (32 per cent)[1,3]. They are characterized by a microcystic appearance with more than six cysts of less than 2 cm in diameter[4]. In addition, there may be central calcification, enhancement around microcysts or of septa, and larger cysts on the periphery of the lesions. Demonstration of these CT signs in typical cases is diagnostic. In practice, outside of centres experienced in pancreatic imaging[4,5] the diagnostic accuracy is between 20 and 40 per cent[1,6]. It is likely that accuracy will improve with the more widespread use of spiral CT. The microcystic component of small tumours of 3 cm or less is better demonstrated by endoscopic ultrasonography. Macrocystic forms are present in about 10 per cent of cases and lead to diagnostic difficulty. In this situation examination of cyst fluid can demonstrate typical epithelial cells rich in glycogen and very low levels of tumour markers[7].

Mucinous cystic neoplasms consist of mucinous cystadenomas and mucinous cystadenocarcinomas. They represent 44–49 per cent of cystic tumours[1,3]. The distinction of benign and malignant lesions can be made only by histological examination after pancreatic resection. The risk of malignant progression of mucinous cystadenomas is probably high but difficult to determine. These tumours typically consist of large cysts with septa, peripheral calcification and sometimes a solid intracystic component. Demonstration of a large multilocular cyst should lead to surgical resection without any other investigation. A large unilocular cyst without preceding pancreatitis and with an otherwise normal pancreas is most likely a mucinous pancreatic neoplasm. If there is a history of acute pancreatitis (which can complicate mucinous tumours), examination of cyst fluid can discriminate between tumour and pseudocyst. Biochemical examination of cyst fluid in mucinous neoplasms shows very low levels of pancreatic enzymes and high levels of tumour markers[7]. The presence of mucin-containing or malignant cells is conclusive. Nevertheless there remains a considerable risk of diagnostic overlap with pseudocyst; 9 per cent for mucinous cystadenomas and 15 per cent for cystadenocarcinomas[1]. This risk increases when the cystic tumour communicates through the pancreatic duct (7 per cent of cystadenomas and 10 per cent of cystadenocarcinomas).

Intraductal papillary and mucinous tumours have been defined recently, and represent 11 per cent of cystic tumours[1,3]. In these tumours the cysts are in fact dilated main pancreatic duct or secondary branches of the duct. The duct lining produces a mucus secretion which fills the duct lumen. The mucosa shows changes of adenoma with dysplasia, or adenocarcinoma. The duct dilatation may be demonstrated by endoscopic ultrasonography or CT and there is no evident obstructing lesion. Duodenoscopy typically shows mucus oozing from the major papilla, and pancreatography demonstrates numerous plugs in the dilated pancreatic ducts. These appearances make diagnosis of intraductal tumour difficult. Magnetic resonance pancreatography and pancreatoscopy may allow localization of the tumour; this may permit partial pancreatic resection.

Pseudopapillary and solid tumours represent 4 per cent of cystic tumours[1,3]. Despite their name, they contain cystic areas consisting of regions of haemorrhage and necrosis. The diagnosis should be considered when there is a large tumour with solid and cystic areas often with calcification, with a capsule, and presenting in a young woman or adolescent. Magnetic resonance imaging appears superior to CT for the diagnosis of these tumours[8].

Treatment of epithelial cystic tumours of the pancreas should be related to the histological grade. Serous cystadenomas are benign tumours; malignant serous cystadenocarcinomas are exceptional[9]. Conservative management is wholly justified for a well documented serous cystadenoma with no symptoms and without duct or vascular obstruction. The patient should be followed by annual ultrasonography because some tumours unpredictably develop complications. In other cases, pancreatic resection taking account of the benign nature of the tumour should be performed. Mucinous cystadenomas should be resected completely, which is often relatively straightforward given the preponderance of distal lesions (72–80 per cent). Cystadenocarcinomas are often resectable (up to 73 per cent[1]) but may involve the resection of neighbouring organs and, if necessary, the portal vein. These extensive resections are justified as the 5-year survival rate may exceed 50 per cent[1,10]. Adjuvant therapy should be considered for aneuploid tumours. Papillary and mucinous intraductal tumours should be resected to remove all the adenomatous or malignant mucosa, in order to avoid recurrence in the pancreatic remnant. Peroperative pancreatoscopy and frozen-section examination of the resection margin are useful in determining the extent of resection, which may need to be total. Finally, pseudopapillary solid cystic tumour should be considered potentially malignant and should be resected completely.

There remain several unanswered questions. Mucinous cystic tumours which communicate with the pancreatic duct are not clearly distinguished from intraductal tumours. The epidemiological differences between mucinous cystadenomas and cystadenocarcinomas call into question the link between these two lesions. The long-term outcome of the ductal system after partial pancreatectomy for intraductal tumours is unknown, as is the risk of subsequent metastases after resection of a pseudopapillary solid tumour; some cases have been reported.

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Skull radiographs and children with blunt head injury

Assessing children for possible intracranial injury following blunt head trauma often is difficult. Children with an impaired level of consciousness or focal neurological signs are relatively easy to identify, but many have non-specific symptoms of headache, vomiting or drowsiness, with no focal neurological signs. Such symptoms occur with and without intracranial injury and may be difficult to interpret. In the UK, skull radiographs are used widely to select children who have a skull fracture for admission to hospital or for computed tomography (CT) of the head. This is based on evidence from retrospective studies, notably that of Teasdale *et al.*[1], which suggests that a skull fracture is a risk factor for intracranial haematoma. However, this approach is not accepted universally[2,3], particularly because major intracranial injury may occur in children in the absence of a skull fracture; in the report by Teasdale *et al.*[1], 38 per cent of those with intracranial haematoma did not have a skull fracture.

Under the age of 2 years, the routine use of skull radiography is justified because of the high risk of non-accidental injury in this age group. The nature of the skull fracture and the presence of old injuries may be important clues as to the cause of the injury. It is in older children that the role of skull radiography is controversial.

The results of two relevant prospective studies have been published recently. One was a study of 9269 children with blunt head trauma who attended the Accident and Emergency Department at Alder Hey Children's Hospital in Liverpool[4,5]. Of these, 6011 had a skull radiograph; 161 (2·7 per cent) skull fractures were revealed. A head CT scan was carried out in children with a radiologically evident fracture and in those without a fracture if there were neurological indications for such a scan.

Almost a quarter (23 per cent) of the skull fractures were missed by accident and emergency surgical staff who assessed the initial radiographs, and there were nine false-positive diagnoses of fracture. Sixty-four patients with no neurological abnormality had a head CT scan because a skull fracture had been identified; only one scan showed an intracranial abnormality and this was of no clinical significance. Seventy-seven patients underwent head CT because of neurological abnormality and 16 scans showed an intracranial abnormality, four in children without a fracture. Four patients died, only one of whom had a skull fracture.

In summary, intracranial injury occurred in patients with or without skull fracture and all those with a clinically significant injury had neurological indications for CT. These indications were altered level of consciousness, focal neurological abnormality or persistent/progressive symptoms. For prediction of intracranial injury the sensitivities of skull radiography and neurological abnormality were 65 and 91 per cent respectively. The negative predictive values were 83 and 99 per cent respectively.

The second report, from St Louis Children's Hospital in Missouri, was a prospective study of 322 children with 'non-trivial' head injury, defined as injury associated with neurological symptoms or signs[6]. Fifty children (16 per cent) had a skull fracture; intracranial injury occurred in 27 (8 per cent), of whom 13 did not have a skull fracture. In general, the authors' conclusions and recommendations were in agreement with those of the Liverpool group, with the exception that Quayle *et al.* concluded that 16 of their 27 patients with intracranial injury were neurologically normal, defined as having normal mental status and no focal neurological abnormality. However, ten of these children were aged 2 years or more and all had one or more symptoms of brain injury, namely headache, vomiting, amnesia, dizziness or drowsiness. Using the Liverpool criteria, all of these patients would have been admitted to hospital and all those with a clinically significant intracranial abnormality would have had a CT scan.

These two reports support the argument that the skull radiograph is not a reliable triage tool for children following blunt head trauma. Although an intracranial injury is more likely to occur when the skull is fractured, severe injuries occur without a skull fracture and the skull radiograph cannot be justified rationally as a tool for diagnostic exclusion. Patients in whom symptoms of possible neurological injury, notably headache, vomiting and drowsiness, are the only abnormal findings should be observed in the accident and emergency department. Most will recover within a few hours and may be allowed home with written guidelines for recognizing and reacting to signs of evolving lesions. Those whose symptoms persist beyond 6–8 h should be admitted to hospital for further observation. If the symptoms continue and, particularly, if they become progressively more severe, an urgent head CT scan is indicated. A skull radiograph does not contribute to this care pathway and should be restricted to patients with suspected non-accidental injury, penetrating injury or depressed fracture.

Radiographs may continue to be requested by those who fear possible medicolegal consequences if, for example, a patient who is sent home from the accident and emergency department without having a radiograph is subsequently found to have an intracranial haematoma. There is no simple answer to this. The Bolam ruling (1957)[7] would support a practice accepted as proper by a 'responsible body of medical men'. The most recent authority on this, the House of Lord's decision in Bolitho (1997)[8], focuses on the risk/benefit ratio of an intervention. This is an arena which requires further legal exploration.

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Review

Antibiotic prophylaxis in the initial management of severe acute pancreatitis

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Background The role of antibiotic prophylaxis in the initial management of patients with acute pancreatitis is an area of major controversy. Contrary to earlier clinical trials, recent experimental and clinical studies have accrued evidence that warrants reappraisal of current clinical practice. This article reviews these recent advances in knowledge.

Methods All papers derived from a Medline search for the years 1990–1997 inclusive using the text words 'acute', 'pancreatitis', 'antibiotic' and 'antibiotics' were studied. Additional papers were derived from reference lists within papers identified by the Medline search. Only experimental and clinical papers relevant to the issue of prophylactic antibiotic therapy in acute pancreatitis are included in the review.

Results and conclusion Current experimental evidence favours the use of prophylactic antibiotics in severe acute pancreatitis. The results of contemporary randomized clinical trials restricted to patients with prognostically severe acute pancreatitis have demonstrated improvement in outcome associated with antibiotic treatment.

The results of three prospective randomized clinical studies of antibiotic prophylaxis in severe acute pancreatitis provide evidence of a role for antimicrobial therapy as part of initial treatment in this condition[1–3]. Nevertheless, controversy persists about the strength of evidence for antibiotic therapy and in a recent review Barie[4] stated that 'the data are insufficiently strong to mandate prophylaxis or elevate it to the standard of care'. However, given the rapid rate of accrual of evidence, Barie's statement and the evidence base on which it was made require reappraisal. This need is made more pressing by the fact that if his statement were to be accepted widely, a potentially valuable therapeutic option in the management of a disease with relatively few specific treatment modalities could be lost. This article reviews recent experimental and clinical studies relating to antibiotic prophylaxis in acute pancreatitis.

Methods

A Medline search was carried out for the period 1990–1997 inclusive using the textwords 'acute', 'pancreatitis', 'antibiotic' and 'antibiotics'. In addition, a search using generic drug names was carried out to identify studies in which specific antibiotics were used. Articles identified from these two searches were studied. Further articles relating to the use of prophylactic antibiotics in acute pancreatitis were identified from the reference lists of papers identified previously through the Medline searches. Papers with data relating to antibiotic penetration into human pancreatic tissue, studies of prophylactic antibiotics in experimental acute pancreatitis and clinical trials in human acute pancreatitis were studied.

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Bacterial involvement in acute pancreatitis

Local pancreatic infection occurs in 30 per cent of patients with severe acute pancreatitis and is associated with significant morbidity and mortality rates[5]. Although pancreatic infection comprises two somewhat distinct clinical entities, pancreatic abscess and infected pancreatic necrosis, the organisms found in each condition are generally similar[6–8]. Data relating to secondary microbial infection in acute pancreatitis are difficult to interpret and compare, because of the lack of standardization in nomenclature before the 1992 Atlanta consensus conference[9]. Earlier data are also affected by the difficulties of culturing anaerobic species. With these limitations in mind, microbiology results demonstrating organisms cultured from patients with infective complications of acute pancreatitis are shown in *Table 1*.

The important organisms appear to be aerobic Gram-negative bacilli, in particular *Escherichia coli*, with a significant number of cases involving *Enterococcus* spp. and *Staphylococcus* spp. Fungal infection is uncommon, but increased antibiotic usage may modify prevalence. Polymicrobial infection occurs more frequently in pancreatic abscesses than in infected pancreatic necrosis[6] and more often involves an *Enterococcus* sp.[13].

The recognition that colonic type bacteria frequently cause pancreatic infection has led to the theory that the gut acts as a reservoir from which bacteria can translocate to colonize pancreatic necrosis and acute fluid collections, resulting in infected pancreatic necrosis and pancreatic abscesses. Experimental studies appear to support this theory. Transient bacterial colonization of proximal small bowel occurs in a rat bile duct ligation model of acute pancreatitis and results in increased rates of bacterial translocation[14,15]. Furthermore, Widdison[16] in a series of experiments with a feline model of acute pancreatitis demonstrated that bacteria are able to reach the pancreas from the colon by direct transmural spread.

Table 1 Organisms associated with secondary infection in acute pancreatitis

Reference	Year	Nature	Mono	Poly	*Escherichia coli*	*Pseudomonas*	Other coliforms	*Staphylococcus*	*Enterococcus*	Fungus	Anaerobes
Miller *et al.*[10]	1974	Pancreatic abscess	57	43	36	13	55	15	21	—	—
Beger *et al.*[11]	1986	Infected necrosis	—	—	53	11	56	11	13	7	11
Bittner *et al.*[6]	1987	Infected necrosis	77	23	50	—	~ 50	—	—	—	—
Bittner *et al.*[6]	1987	Pancreatic abscess	56	44	50	—	~ 50	—	—	—	—
Fedorak *et al.*[7]	1992	Infected necrosis	43	57	24	14	34	57	33	19	9
Fedorak *et al.*[7]	1992	Pancreatic abscess	40	60	30	20	80	30	40	5	15
Fedorak *et al.*[7]	1992	Infected pseudocyst	78	22	35	0	26	17	13	9	4
Bradley[8]	1993	Infected necrosis	66	34	47	10	34	2	3	6	—
Banks *et al.*[12]	1995	Pancreatic infection	—	—	23	4	37	25	14	4	4

Values are percentages of cases with each organism. Infective complications are classified using Atlanta consensus conference terminology[9]. Mono, Monomicrobial infection; Poly, polymicrobial infection

Translocation may also be important in the pathogenesis of the organ dysfunction that can complicate acute pancreatitis. Endotoxin, a lipopolysaccharide derived from the outer membrane of Gram-negative bacteria and a potent activator of inflammation, can be detected in the serum of patients with severe acute pancreatitis[17] and its presence is related to organ failure[18]. Windsor and colleagues[19] found that depletion, or significant falls in levels, of serum antiendotoxin immunoglobulin G antibody, believed to be secondary to exposure to endotoxin, correlated with the development of multiple organ failure in acute pancreatitis.

Penetration of antibiotics into human pancreatic tissue

Roberts and Williams[20] investigated the penetration of ampicillin into pancreatic tissue by sampling pancreatic ductal fluid at endoscopic retrograde cholangiopancreatography in ten patients given a loading dose of parenteral ampicillin. In six of seven subjects ampicillin was undetectable in the fluid. This indirect evidence of poor penetration of ampicillin into pancreatic tissue is lent further credence by the work of Trudel *et al.*[21], which demonstrated that ampicillin does not achieve bactericidal concentrations in pancreatic tissue in a canine model of acute pancreatitis.

Buchler and co-workers[22] compared human pancreatic tissue concentrations of ten bactericidal antibiotics administered intravenously in 89 patients undergoing pancreatic surgery to determine probable antibiotic efficacy in pancreatic infection. Antibiotic efficacy was estimated with reference to the antibiotic tissue concentration attained and the effect of that tissue concentration upon the types of organisms commonly involved in pancreatic infection. On this basis the antibiotics were divided into three groups. Group A consisted of the aminoglycosides, which failed to reach the minimum inhibitory concentration (MIC). Group B antibiotics reached tissue concentrations that were effective against some but not all organisms and included the extended-spectrum penicillins, mezlocillin and piperacillin, and the third generation cephalosporins, ceftizoxime and cefotaxime. Group C antibiotics consisted of the 4-quinolones and imipenem which reached tissue concentrations that were bactericidal for most infecting organisms. However, only eight of the samples were obtained from patients with acute pancreatitis and it is possible that patterns of antibiotic penetration in inflamed human pancreas are different.

Foitzik and colleagues[23] have demonstrated, in a rat model of acute pancreatitis, that pancreatic capillary blood flow and pancreatic oedema have marked effects on the pancreatic tissue concentration of parenterally administered cefotaxime, but not on pancreatic tissue concentrations of imipenem. Koch and colleagues[24] confirmed in a study of ofloxacin that the 4-quinolone class of antibiotics achieves bactericidal levels in normal pancreas, inflamed pancreatic tissue and pancreatic necrosis. Similarly, confirming that the third generation cephalosporins have good pancreatic penetration, Drewelow and colleagues[25] found that ceftazidime achieved antimicrobial tissue concentrations in both viable and necrotic pancreatic tissue in three human patients with acute necrotizing pancreatitis.

Bassi and co-workers[26] examined the penetration of aminoglycosides, perfloxacin, imipenem, mezlocillin and metronidazole into microbiologically proven infected pancreatic necrosis in humans. Following parenteral administration of antibiotics, pancreatic tissue samples were collected at the time of pancreatic necrosectomy or by computed tomography (CT)-guided needle aspiration. Although all of the antibiotics could be detected in necrotic tissue, only perfloxacin and metronidazole consistently attained levels greater than the MIC for organisms found in pancreatic infection. Mezlocillin and imipenem inconsistently attained levels greater than the MIC, although tissue concentrations of imipenem were increased by repeated administration. Aminoglycoside levels were always inadequate.

In summary, it appears that the third generation cephalosporins, piperacillin, mezlocillin, 4-quinolones, imipenem and metronidazole achieve useful pancreatic tissue concentrations, while the aminopenicillins, first generation cephalosporins and the aminoglycosides do not. However complex pathophysiological mechanisms may exist in the inflamed pancreas altering the pharmacokinetics of antibiotics.

Experimental evidence for antibiotic therapy in severe acute pancreatitis

The potential benefits of prophylactic antibiotics in the prevention of pancreatic infection complicating acute pancreatitis have been demonstrated in experimental studies. Foitzik and colleagues[27] studied the effects of intravenous and oral antibiotics in a rat model of severe acute pancreatitis induced by a combination of low-dose intraductal infusion of glycodeoxycholic acid superimposed on intravenous caerulein hyperstimulation. At 6 h, animals were randomly allocated into five treatment groups: controls, intravenous cefotaxime, intravenous imipenem, oral antibiotics (polymyxin E, tobramycin and amphotericin) and full gut decontamination (oral antibiotics plus intravenous cefotaxime). No treatment regimen affected the mortality rate at 96 h. At this time point, surviving animals were sacrificed for quantitative bacterial studies of the caecum, pancreas and kidney. Pancreatic bacterial counts were reduced by the intravenous imipenem and full-gut decontamination regimens but not by oral antibiotics or intravenous cefotaxime alone. Interestingly, although intravenous cefotaxime reduced rates of pancreatic infection by *E. coli*, this was compensated for by a rise in enterococcal infection. The failure to demonstrate a survival benefit from the prevention of pancreatic infection following intravenous imipenem or full-gut decontamination probably reflects the short follow-up, with early deaths arising from the primary physiological insult of acute pancreatitis rather than the effects of secondary pancreatic infection.

Similarly, in a feline model of pancreatic infection, Widdison and colleagues[28] demonstrated that intravenous antibiotics were efficacious in the elimination of pancreatic bacterial colonization in acute pancreatitis. Following induction of acute pancreatitis by ductal infusion of glycodeoxycholic acid, *E. coli* placed in the main pancreatic duct resulted in early bacterial colonization. This colonization persisted in animals at 1 week but could be eliminated completely by the use of intravenous cefotaxime started 12 h after the induction of pancreatic infection. No deaths were observed in any study group.

In further experiments with the rat intraductal infusion/caerulein hyperstimulation model of acute pancreatitis, the benefits of intravenous antibiotics over a prolonged period were studied[29]. Following induction of acute pancreatitis, animals were randomized to three groups: control, intravenous ciprofloxacin and intravenous imipenem. Antibiotics were commenced 12 h after the induction of pancreatitis. Disease severity was similar in the three groups as assessed by serum trypsinogen activation peptide assay. At 7 days 75 per cent of rats not receiving antibiotics had pancreatic infection with organisms similar to those found in humans. Imipenem and ciprofloxacin significantly reduced the rates of infection, bacterial counts and number of organisms cultured compared with those in controls. At 21 days, bacterial pancreatic colonization was present in 75 per cent of surviving control animals; although only 35 per cent of animals treated with antibiotics had bacterial colonization, the difference did not reach significance because of the low numbers of surviving animals. There was, however, a significant reduction in the rate of pancreatic abscess formation in antibiotic-treated animals. Most importantly, ciprofloxacin significantly reduced both the 7- and 21-day mortality rates, while imipenem significantly reduced the 21-day mortality rate.

Araida and co-workers[30] demonstrated, in a rat model of acute pancreatitis induced by ductal infusion of meglumine diatrizoate, lipopolysaccharide, taurocholic acid and enterokinase, that the administration of intravenous piperacillin was associated with a significant reduction in incidence of pancreatic infection and 24-h mortality rate.

Controlled clinical studies of antibiotic prophylaxis in severe acute pancreatitis

The use of prophylactic antibiotic therapy in acute pancreatitis is based on the rationale that the prevention of pancreatic infection will result in a reduction in morbidity and mortality rates. However, initial studies of antibiotic prophylaxis in acute pancreatitis were unable to demonstrate a difference in outcome between antibiotic-treated and control groups[31–33]. The failure of early trials to show any benefit was probably due not to a false hypothesis but rather to the use of ampicillin, a drug which is now known not to penetrate pancreatic tissue. Furthermore, these studies did not restrict entry to patients with prognostically severe acute pancreatitis. It is probable that the inclusion of patients with mild disease, who rarely develop pancreatic infection and improve regardless of intervention, reduced the ability of these studies to detect any potential benefit from treatment.

The issue of prophylactic antibiotics was re-addressed in 1993 by Pederzoli and colleagues[1] in a multicentre randomized controlled trial. Seventy-four patients with acute pancreatitis, all prognostically severe by Ranson's criteria[34] and with pancreatic necrosis proven by CT, were randomized to receive either imipenem 0·5 g intravenously at intervals of 8 h for 14 days or to a control group receiving no initial antibiotic therapy. Pancreatic infection was confirmed by positive bacterial cultures obtained by radiologically guided fine-needle aspiration or at operation. Of the control group, ten of 33 developed pancreatic infection, with the risk of developing such infection correlating strongly with the degree of pancreatic necrosis determined by CT. In comparison, despite having a greater degree of pancreatic necrosis, only five of 41 patients treated with imipenem developed pancreatic infection ($P < 0·001$). Furthermore, rates of non-pancreatic infection were also significantly reduced in the antibiotic-treated group. However, antibiotic therapy had no effect on the development of multiple organ failure, the need for operative intervention or on the mortality rate.

Sainio and colleagues[2], in a randomized control trial, studied the use of intravenous cefuroxime in patients with alcohol-induced acute pancreatitis and pancreatic necrosis proven by CT. Sixty patients were randomized either to a group receiving intravenous cefuroxime 1·5 g three times a day from admission until clinical recovery and normalization of serum C-reactive protein concentrations, or to a group in whom antibiotics were commenced only when there was clinical evidence of infection; no significant difference was found in the rate of pancreatic infection between the two groups (nine of 30 *versus* 12 of

30 respectively). However, intravenous cefuroxime appeared significantly to reduce the mean number of infectious complications per patient (1·0 *versus* 1·8 respectively, $P<0·01$), although this appeared to be due mainly to a marked fall in the number of urinary tract infections. Intravenous cefuroxime reduced the requirement for operative intervention (8 *versus* 36 operations respectively, $P=0·012$). Most importantly, there was a significant reduction in the number of deaths in patients treated with cefuroxime (one *versus* seven, $P=0·028$).

Recently, Delcenserie and colleagues[3] randomized 23 patients with alcohol-induced severe acute pancreatitis to either standard medical therapy or standard medical therapy plus intravenous ceftazidime, amikacin and metronidazole. Antibiotic therapy resulted in a significant reduction in the number of patients with proven infection (none *versus* seven, $P<0·03$); there was no significant reduction in the mortality rate. Although this study appears to show a benefit from the use of prophylactic antibiotics, the conclusions to be drawn must be limited because the size of the study sample was small and amikacin, an aminoglycoside, is from a class of drugs that do not penetrate the pancreas.

Following a small randomized controlled trial of 26 patients with pancreatic necrosis proven on CT, Schwarz and colleagues[35] have reported that the combination of ofloxacin and metronidazole administered intravenously lessens the physiological disturbance found in severe acute pancreatitis, but it neither prevented nor delayed the onset of infected pancreatic necrosis.

Interpretation of the message from these four studies requires caution. Reduced mortality rate did not consistently arise from a reduction in pancreatic infection. However, three of the trials did demonstrate a reduction in the rate of pancreatic infection following antibiotic therapy, although this reached statistical significance in only two. These inconsistencies may be a consequence of the relatively small number of patients enrolled in each trial reducing the power of the studies to detect significant differences. As different antibiotic protocols and inclusion criteria were involved, it would be inappropriate to carry out a meta-analysis. If a prospective study of sufficient sample power were to be performed, it would be expected that any demonstrable reduction in the incidence of pancreatic infection with treatment would be associated with a reduced requirement for surgical intervention. This in turn might be expected to translate into a reduction in overall mortality rate.

Choice of antibiotic

Ideally, the choice of antibiotic regimen should be determined by clinical trials. However, in the knowledge that antibiotic therapy is generally beneficial in severe acute pancreatitis and given the absence of direct comparisons between antibiotics, a pragmatic approach must be adopted. Several factors are important in choosing a prophylactic antibiotic, including adequate antibiotic tissue penetration, effectiveness against commonly involved organisms, cost-effectiveness and low incidence of adverse reactions. The important organisms involved in pancreatic infection include coliforms, enterococci, staphylococci and anaerobic bacteria, while the antibiotics that achieve adequate pancreatic tissue levels are the third generation cephalosporins, piperacillin, 4-quinolones, imipenem and metronidazole.

Third generation cephalosporins have a wide spectrum of activity against Gram-negative and Gram-positive organisms. Although different drugs in this category are generally active against similar organisms, some important differences exist, for example cefotaxime and ceftriaxone are less effective than ceftazidime against *Pseudomonas* spp. The third generation cephalosporins are active against staphylococci, albeit to a lesser extent than cefuroxime, a second generation cephalosporin. Interestingly, the pharmacokinetics of cefuroxime relating to pancreatic tissue are unknown and its failure to reduce rates of pancreatic infection in Sainio's study may indicate that pancreatic penetration is poor. Ceftriaxone should probably be avoided because it can form an insoluble salt in bile leading to biliary sludging. This sludging may induce acute pancreatitis[36].

The 4-quinolones (ciprofloxacin and ofloxacin) have high levels of activity against Gram-negative bacteria, including *Pseudomonas* spp., but only moderate activity against Gram-positive bacteria, with a high incidence of resistance among staphylococci. Susceptibility is low amongst anaerobic bacteria. However, the high cost of intravenous ciprofloxacin does not favour its use as routine prophylaxis.

Metronidazole combines anaerobic activity with good penetration into pancreatic tissue[22,26,37]. Although there have been isolated reports of metronidazole-induced acute pancreatitis[38,39], a large retrospective study of prescribed metronidazole found no increased risk from its use[40].

The acylureidopenicillins, piperacillin and mezlocillin, have wide spectrums of activity, including action against *Pseudomonas* spp., *Enterococcus* spp. and anaerobes. Addition of the β-lactamase inhibitor tazobactam increased the spectrum of activity of piperacillin. Again cost considerations restrict the use of intravenous piperacillin/tazobactam.

The carbapenem group of antibiotics, including imipenem, has a very broad spectrum including activity against *Pseudomonas* spp., *Staphylococcus* spp. and *Enterococcus* spp. and achieves good penetration into pancreatic tissue[22,26]. As resistance to this group remains uncommon, the use of its component drugs is at present confined to second-line therapy in serious infection. This, together with the high cost of therapy, makes routine use of this drug grouping as prophylaxis inappropriate.

Prophylaxis against infection by *Enterococcus* spp. is problematic. Not only is antibiotic resistance in enterococci becoming increasingly common[41,42], the current therapeutic regimen of choice, ampicillin alone or in combination with gentamicin, employs antibiotics with poor penetration into pancreatic tissue, while the second-line chemotherapeutic agent vancomycin has potentially serious side-effects and no data exist regarding its penetration into the pancreas. Piperacillin and imipenem have useful activity against *Enterococcus* spp. Prophylaxis against *S. epidermidis* is similarly complicated. *Staphylococcus epidermidis* is often sensitive to cephalosporins, but unpredictable multidrug resistance occurs[43].

Alternative strategies: selective decontamination of the gut

Intravenous antibiotic prophylaxis in acute pancreatitis is based on the belief that adequate pancreatic tissue levels of antibiotics can prevent colonization of the inflamed pancreas following translocation of organisms from the gut. Selective gut decontamination with oral antibiotics is an alternative strategy, aimed at eliminating pathogenic intestinal flora to reduce bacterial translocation, thereby reducing the risk of pancreatic infection.

As previously discussed, Foitzik and co-workers[27] demonstrated that oral antibiotics alter normal intestinal flora and, when combined with intravenous antibiotics, lead to a reduction in the rate of pancreatic infection. Similarly, in a mouse model of severe acute pancreatitis induced by a choline-deficient diet supplemented with 0·5 per cent DL-ethionine Isaji and colleagues[44] demonstrated that therapy with oral bacitracin, metronidazole and neomycin antibiotics resulted in reduced rates of positive bacterial cultures from samples of peripheral blood, ascites, spleen and pancreas, and significantly improved survival. Interestingly, Gianotti and colleagues[45] have evaluated several different gut decontamination regimens in a mouse model of acute pancreatitis. Although all decontamination regimens resulted in significant reductions in bacterial flora, not all were associated with decreased rates of bacterial translocation and reduced mortality rates, suggesting that the benefits of gut decontamination do not arise solely from the elimination of pathogenic intestinal bacteria.

Luiten and colleagues[46] evaluated the role of selective gut decontamination in patients with severe acute pancreatitis. In a multicentre trial, 102 patients with prognostically severe acute pancreatitis as defined by multiple laboratory criteria (Blamey and colleagues[47]) and/or contrast-enhanced CT scoring (Balthazar *et al.*[48]) were randomized to either conventional therapy or conventional therapy supplemented with selective gut decontamination using oral and rectal colistin, amphotericin and norfloxacin. In addition, patients in the selective gut decontamination group received intravenous cefotaxime until aerobic Gram-negative bacteria were eliminated from the oral cavity and rectum. Although there was a reduction in mortality rate from 35 per cent in the control group to 22 per cent in the group given selective decontamination, this did not reach statistical significance. However, when allowing for differences in disease severity, multivariate analysis suggested a significant survival benefit following gut decontamination ($P = 0{\cdot}048$). Encouragingly, selective gut decontamination reduced the rate of pancreatic infection compared with that of the control group (38 *versus* 18 per cent, $P = 0{\cdot}03$).

Discussion

Infected pancreatic necrosis and pancreatic abscess remain feared complications of severe acute pancreatitis because of the attendant increase in the risk of death and the requirement for surgical intervention[11]. Despite improvements in intensive care medicine and surgical practice, the problem continues[49]. Early attempts at preventing the development of pancreatic infection by using antibiotic prophylaxis foundered because of improper patient selection and inappropriate antibiotic usage. However, based on improved knowledge of the pathogenetic mechanisms of the disease and better understanding of antibiotic pharmacokinetics, recent clinical trials have demonstrated a benefit from antibiotic prophylaxis in severe acute pancreatitis[50]. Unfortunately, doubts about its effectiveness persist. The recent American College of Gastroenterology practice guidelines[51] merely state that it is 'reasonable to initiate' antibiotic therapy in severe acute pancreatitis, while Barie[4] in his review is more critical of the present evidence.

Following consideration of the organisms implicated in pancreatic infection, the evidence upon which the merit of prophylactic antibiotics in acute pancreatitis must be judged has been reviewed. It is concluded that, in contrast to Barie's statement, there is experimental and clinical evidence to suggest that current practice in patients with severe acute pancreatitis should incorporate prophylactic antibiotic therapy. However, the weight of this evidence is reduced by the fact that the four small prospective clinical studies available have not shown a consistent reduction in pancreatic infection. There is, to date, no large-scale prospective study of sufficient sample power to make the use of antibiotic prophylaxis mandatory.

The authors agree with Johnson[50] that therapeutic issues remain, particularly in determination of the ideal antibiotic and the duration of therapy. However, appropriate studies to define these variables may be difficult to undertake. Assuming 30 per cent of patients with prognostically severe acute pancreatitis develop infected pancreatic necrosis, a total sample size of 322 is required to detect a 50 per cent reduction, assuming a two-tailed test with significance level of 5 per cent and a study power of 90 per cent. Even larger studies would be required to evaluate reductions in mortality rate. Furthermore, the stage of clinical equipoise between prophylactic antibiotic therapy and no antimicrobial therapy has almost certainly passed; clinicians may be reluctant to enter patients with severe acute pancreatitis into studies involving a 'no antibiotic' arm. Although less than satisfactory, further evidence may have to derive from observational studies. Ho and Frey[52] have recently published a retrospective study suggesting a reduction in the rate of pancreatic infection, in patients with prognostically severe acute pancreatitis admitted to their institution, following the introduction of a policy of prophylactic administration of intravenous imipenem for 4 weeks.

In summary, although the rationale for continuing investigation of the value of antibiotic therapy in severe acute pancreatitis is clear, Barie's[4] notion that more studies of this therapeutic modality are required to address the 'myriad issues yet to be resolved' is impractical. In a common and often fatal disease such as acute pancreatitis, where there is a paucity of rational therapeutic interventions, the loss of a potentially valuable therapy such as antibiotic prophylaxis would be unfortunate.

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Review

Diagnosis and treatment of sphincter of Oddi dysfunction

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Background Sphincter of Oddi dysfunction is a challenge from both the diagnostic and therapeutic point of view. There is much ongoing debate about the accuracy and usefulness of various diagnostic tests, as there is about the effectiveness of proposed therapeutic alternatives.

Methods A comprehensive review of the past 15 years' literature was undertaken, using the Medline database and cross-referencing of major articles on the subject.

Results and conclusion Endoscopic and surgical treatments result in similar outcomes, with considerable failure rates. The latter reflect the difficulties in accurate diagnosis and a lack of sound objective criteria for selecting patients for intervention. In addition, in some patients sphincter of Oddi dysfunction may be only part of a generalized motility disorder of the gastrointestinal tract.

The sphincter of Oddi is a complex muscular structure consisting of smooth muscle fibres that surround the distal common bile duct (CBD), pancreatic duct and ampulla of Vater (the common channel of both ducts)[1–3]. It is 6–10 mm in length and is situated almost entirely in the wall of the duodenum, traversing it obliquely[4,5]. It is composed of small muscular segments, described by Boyden[4] in a detailed study: the sphincter choledochus (which surrounds the distal CBD), the sphincter pancreaticus (which surrounds the lower end of the pancreatic duct) and the sphincter ampullae (which surrounds the common channel or ampulla). The most important element seems to be the sphincter choledochus; the sphincter pancreaticus is identified in only 10 per cent of specimens[4].

This group of smooth muscle fibres is functionally independent of duodenal muscle and its primary function is to control the delivery of bile and pancreatic juice into the duodenum. This sphincter also diverts bile into the gallbladder and prevents retrograde reflux of duodenal luminal fluid into the ducts[1]. Bile flow occurs mainly by a passive mechanism between phasic contractions, the contractions serving to propel a small bolus of fluid to clear the ductal opening[5]. Understanding of sphincter of Oddi function relied initially on information obtained from the intraoperative measurement of CBD duct pressure and flow of contrast agent through the papilla using a debimanometer, as described by Tondelli and Gyr[6]. Subsequent use of endoscopic manometry has enhanced understanding of both normal and abnormal sphincter function. Today, the sphincter of Oddi is believed to be a more dynamic structure than it was thought to be in the past. Sphincter motility differs in fasting, when it is integrated with the migrating motor complex (MMC), and the postprandial state, when the control mechanisms of motility are unclear.

The MMC pattern of gastrointestinal motility during fasting propagates from the distal oesophagus[7,8] to the ileum periodically every 90–120 min and is divided into four phases. Bile flow into the duodenum during fasting occurs in a cyclical pattern in concert with the MMC phases, to reach a maximum during the latter portion of the MMC[9]. The frequency of myoelectrical spike potentials of the sphincter of Oddi increases gradually from phase I to a maximum in phase III and then decreases rapidly during phase IV. This may represent a preventive mechanism against accumulation of biliary microcrystals and debris, and the creation of calculi, during fasting.

After food the pattern of gastrointestinal motility changes and the sphincter of Oddi mirrors these changes by irregular bursts of spike potentials. The frequency of spike potentials depends on the type and amount of food ingested, fat and proteins causing the greatest frequency of sphincteric activity[9].

What is dysfunction of the sphincter of Oddi?

Many articles have been published in the past two decades about the clinical syndrome described as 'dysfunction of the sphincter of Oddi'. Such dysfunction could affect the biliary duct leading to pain characteristic of biliary colic, or the pancreatic duct causing recurrent acute pancreatitis. The clinical syndrome is poorly defined, incompletely understood and difficult to diagnose. A number of terms have been used to describe the same clinical entity (e.g. papillary stenosis, sclerosing papillitis, biliary spasms, biliary dyskinesia, postcholecystectomy syndrome) which has resulted in some confusion. Recently, to avoid such confusion, two types of sphincter of Oddi dysfunction have been proposed on the basis of pathogenic mechanism[10,11].

Sphincter of Oddi stenosis

Sphincter of Oddi stenosis is a structural abnormality in which there is narrowing of part or all of the sphincter due to chronic inflammation and fibrosis. It is associated with pancreatitis or injury from gallstone migration through the papilla, trauma from intraoperative manipulation of the CBD or non-specific inflammatory conditions, such as adenomyosis. This structural abnormality is further associated with raised basal sphincter pressure and alteration of phasic contractions measured by endoscopic manometry.

Sphincter of Oddi dyskinesia

Sphincter of Oddi dyskinesia is an intermittent functional blockage of the high-pressure zone of the sphincter. It

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results from spasm, hypertrophy or denervation of the sphincter muscle. This condition may reflect a motility disorder of the sphincter similar to motility disorders elsewhere in the gastrointestinal tract (e.g. hypertensive lower oesophageal sphincter). Basal pressure is raised but, unlike in structural stenosis, it may be reduced by the administration of smooth muscle relaxants (nitrates). However, there is still a significant overlap in the manometric values found in both types of sphincter of Oddi dysfunction.

Diagnosis of sphincter of Oddi dysfunction

Sphincter of Oddi dysfunction should be suspected in patients with pain of apparent biliary or pancreatic origin, in the absence of an organic cause (after conventional investigations). Twenty-nine per cent of patients with unexplained right upper quadrant abdominal pain who have a normal extrahepatobiliary and pancreatic system have manometric evidence of sphincter of Oddi dysfunction[12]. It is difficult to assess accurately the incidence in the general population. In many cases the diagnosis is somewhat arbitrary and difficult to prove, but it is estimated that it occurs in 0·88 per cent of those undergoing cholecystectomy[13]. Cholecystectomy may reveal previously unrecognized pre-existing symptoms due to sphincter of Oddi dysfunction because there is no longer a gallbladder to serve as a reservoir to accommodate pressure and volumetric changes[14]. However, there is little doubt that in most cases symptoms after cholecystectomy are non-biliary in origin[15]. The true incidence of sphincter of Oddi dysfunction as a cause of recurrent acute or chronic pancreatitis is impossible to estimate, but an association exists between sphincter dysfunction and pancreatic disease. Abnormal manometric findings in patients with early minimal-change chronic pancreatitis have been reported recently[16] and, when other common causes of pancreatitis have been excluded, sphincter dysfunction should be considered in the differential diagnosis. Numerous tests have been proposed to obtain an accurate diagnosis, but they are insensitive and non-specific.

Hogan and Geenen[17] have suggested a classification for suspected sphincter of Oddi dysfunction known as the Milwaukee Biliary Group Classification (*Table 1*). This seeks to outline an optimal scheme for investigation and to predict the outcome of endoscopic sphincterotomy or surgical sphincteroplasty. Sherman *et al.*[18] have described a similar classification for pancreatic type pain (*Table 2*).

After cholecystectomy, a dilated CBD detected by ultrasonography has been proposed as a feature of sphincter of Oddi dysfunction[19] which has high predictive value for favourable outcome after sphincterotomy[20]. However, it is a non-specific feature which can be detected in 4 per cent of asymptomatic patients after cholecystectomy[21,22]. In addition, the diameter of the CBD varies with the age of the patient[9]. Determination of the increase in duct diameter after a fatty meal or cholecystokinin octapeptide may be useful in the evaluation of the function of the sphincter of Oddi[23,24]. No increase in diameter after provocation, measured by ultrasonography, should occur in normal subjects, because normal changes in sphincter motility should enhance bile flow into the duodenum and decrease the diameter of the CBD[11]. A paradoxical increase in CBD diameter reflects an abnormal resistance to bile outflow and an increase greater than 2 mm is observed in patients with sphincter dysfunction[23].

Table 1 Milwaukee Biliary Group Classification, after Hogan and Geenen[17]

	Biliary type pain	Abnormal liver function test results*	Dilated common bile duct†	Delayed drainage‡
Type I	+	+	+	+
Type II	+	One or two of the above		
Type III	+	None of the above		

*Alanine transaminase and aspartate transaminase levels more than two times normal value, on at least two occasions; †more than 12 mm on ultrasonography or 10 mm on endoscopic retrograde cholangiopancreatography; ‡more than 45 min on ERCP in the supine position

Table 2 Pancreatic type pain classification, after Sherman *et al.*[18]

	Recurrent pancreatitis and/or typical pancreatic pain	Abnormal enzymes*	Dilated pancreatic duct†	Delayed drainage‡
Type I	+	+	+	+
Type II	+	One or two of the above three		
Type III	+	None of the above three		

*More than 1·5–2 times the upper limit; †greater than 6 mm in the head and more than 5 mm in the body on endoscopic retrograde cholangiopancreatography; ‡more than 9 min

A similar ultrasonographic method has been proposed for the evaluation of the pancreatic component of the sphincter of Oddi. The diameter of the pancreatic duct in normal individuals measures less than 1 mm. Following secretin injection, there is a temporary increase in pancreatic duct diameter that lasts for less than 30 min. A diameter greater than 1·5 mm at 30 min suggests a resistance to the outflow of pancreatic juice[25]. This test is operator dependent for evaluation and interpretation but it is non-invasive, easy to apply and inexpensive. It is useful as a screening investigation and may alert the physician to the possibility of sphincter of Oddi dysfunction[11].

Another commonly used measure of sphincter dysfunction is delayed emptying of the CBD at endoscopic retrograde cholangiopancreatography (ERCP). ERCP is one of the first-line investigations of symptoms of hepatobiliary and pancreatic origin. It is an excellent test that gives the most accurate image of both biliary and pancreatic ducts. It is a useful tool to exclude CBD obstruction caused by stone or stricture, or to demonstrate a congenital abnormality, such as pancreas divisum[26]. Failure to cannulate either duct may raise suspicion that an anatomical deformity exists[26] but interpretation is subjective and operator dependent. Reproduction of pain during injection of contrast medium has not been generally accepted as a reliable indicator of sphincter dysfunction. The papilla may appear normal at ERCP or at the time of intraoperative inspection, despite the presence of marked fibrosis[26]. Delay in emptying of contrast medium for more than 45 min is consistent with sphincteric dysfunction[19,27] and has a high predictive value for favourable outcome after sphincterotomy[20]. The test is, however, poorly standardized, because during ERCP varying amounts of contrast agent may be injected into the biliary tree and differing amounts of sedative, potentially affecting sphincter motility, may be administered[2,10]. The invasive nature of ERCP and the use of sedation are the main disadvantages of the procedure.

Dynamic hepatobiliary scintigraphy has been used as a non-invasive tool for evaluation of the sphincter of Oddi by providing indirect evidence of increased sphincter resistance. This method can be standardized, and can give quantitative and qualitative information by measuring a significant delay in hepatic uptake and washout[2,28]. It has high sensitivity and should be used as an early diagnostic tool to evaluate suspected sphincter dysfunction[9] after a structural lesion of the CBD has been excluded[2]. The hilar time–activity curve and the 45-min clearance value are the most useful criteria for differentiating between partial biliary obstruction and normality[29]. Nevertheless, in a large proportion of patients with sphincter dysfunction it fails to detect any abnormality, and there is a considerable overlap with the normal population[14]. The test cannot differentiate parenchymal liver disease, intrahepatic cholestasis and extrahepatic bile duct pathology[2,9]. It is useful for providing information about the biliary component of the sphincter but it does not help in pancreatic pain. The episodic nature of the disorder, especially dyskinesia, means that abnormal scintigraphy is unusual when the procedure is performed in a patient who is currently free of pain[30]. This has led some to use scintigraphic techniques after stimulation with cholecystokinin, and a scoring system has been proposed which combines visual and quantitative criteria for the diagnosis of sphincter dysfunction[28]. Cholecystokinin has been used as a functional stimulus to accentuate differences in bile flow rates between a normal postcholecystectomy population and those with sphincter of Oddi dysfunction. The scoring system incorporates all the variables previously demonstrated to be of significance in the diagnosis of sphincter dysfunction: time of peak liver activity, time at which the intrahepatic biliary tree is first visualized, prominence or dilatation of the biliary tree, time at which the bowel is first visualized, percentage of CBD emptying and CBD:liver ratio. This score appeared to be superior to previous diagnostic criteria and attained a perfect separation between patients with sphincter of Oddi dysfunction and controls (sensitivity 100 per cent, specificity 100 per cent)[28].

A series of provocation tests has been used with equivocal results and debatable usefulness. The most widely known, using various methodologies, is the morphine–prostigmine provocation test (Nardi test)[31]. This test is performed by giving an intramuscular injection of morphine 10 mg and prostigmine 1 mg to produce simultaneously spasm of the sphincter of Oddi and stimulation of exocrine pancreatic secretion. Reproduction of the patient's pain and/or increase in pancreatic or liver-associated enzymes are required for a positive result. This test also identifies those who are most likely to benefit from sphincteroplasty and septectomy[31]. Abnormal responses to morphine–neostigmine in patients with undefined biliary pain have also been reported[32] and there is evidence that the test may be beneficial in chronic relapsing pancreatitis in children[33]. However, other studies have suggested that the method is neither specific nor sensitive for sphincter of Oddi dysfunction[34,35]. These discrepancies of information and interpretation might be due to different methodologies and the varying criteria of positivity used by different authors. The test is cheap and easy to perform but seems to have a low specificity when it is considered alone. It should be used as a screening test in patients with pain of hepatobiliary and pancreatic origin. A combination of scintigraphy and the provocation test has recently been used for postcholecystectomy syndrome[30]. The results were encouraging and showed a good correlation between a positive provocation test and an obstructive pattern on scintigraphy. This combination may be the optimal method for detection of the subgroup of patients with functional abnormality (dyskinesia), but larger studies are required to assess the diagnostic accuracy and predictive value of response to endoscopic or surgical therapy.

Recently there has been a surge of interest in manometry as a diagnostic tool. Three manometric methods have been described: direct endoscopic manometry, indirect manometry and tip transducer manometry[9]. Direct endoscopic manometry is considered the 'gold standard'. It is performed endoscopically through retrograde cannulation of the sphincter with a standard 1·7-mm triple-lumen, side-hole, manometry catheter. The catheter is perfused with distilled water at a low constant flow by a low-compliance perfusion system. The pressure is transmitted constantly through the catheter to external transducers, which transform it to an electrical signal that is amplified and recorded. Selective cannulation of both bile and pancreatic duct is important to evaluate both components of the sphincter, and to exclude any segmental dysfunction responsible for partial biliary obstruction or episodes of acute recurrent pancreatitis[36,37]. The basal pressure of the sphincter of Oddi is usually 5–15 mmHg greater than the pressure in the CBD and 15–30 mmHg greater than that in the duodenum, which is used as zero reference. Phasic contractions of amplitude 50–150 mmHg are superimposed on the basal pressure with a frequency varying between 3 and 8 contractions per min. Most are propagated in an antegrade fashion[9]. Manometric abnormalities ascribed to sphincter of Oddi dysfunction include high basal pressure (more than 40 mmHg), increased amplitude (more than 240 mmHg) or increased frequency (greater than 10 per min) of phasic contractions and increased percentage (more than 50 per cent of the time) of retrograde propagated contractions and paradoxical response to cholecystokinin[10,38–40]. Raised basal pressure appears to be the most consistent, reliable and frequently used variable for therapeutic decision making[3,40]. It has been shown by Geenen *et al.*[41] in a prospective trial that raised basal sphincter pressure is the most reliable finding to predict a successful outcome of endoscopic sphincterotomy. However, others have failed to correlate a favourable outcome with manometric assessment[20,42] and have emphasized that the presence of either a dilated duct or delayed drainage of contrast agent at ERCP predicts a favourable outcome following sphincterotomy[20]. Roberts-Thompson and Toouli[42] in a retrospective series reported good results after endoscopic sphincterotomy in five of eight patients with normal sphincter of Oddi manometry, while seven of 17 patients with abnormal manometric findings (suggesting either stenosis or dyskinesia of the sphincter) failed to have any change in symptoms. They concluded that the results of sphincterotomy appeared to be unrelated to manometric findings.

Several problems occur in the performance and interpretation of biliary manometry. First, the procedure itself is an expensive and sophisticated one, performed in only a few specialized centres. It is quite difficult to carry out, is invasive and requires sedation, which may modify the behaviour of the sphincter. Even an experienced endoscopist may achieve an adequate and complete examination in only 54–87 per cent of patients[13,15,38]. Meshkinpour and Mollot[43] found recently, in a series of 64 patients with postcholecystectomy syndrome, that only 41 per cent had a manometric abnormality. Furthermore, even among patients with type I disease in the Milwaukee classification (the most homogeneous and stringently selected group) 27 per cent had manometric values within the range recorded in healthy volunteers.

Endoscopic biliary manometry also has a higher incidence of associated pancreatitis compared with simple diagnostic ERCP. Approximately 2 per cent of 315 patients undergoing diagnostic ERCP developed pancreatitis compared with four of 21 patients undergoing sphincter manometry[44]. The incidence of postmanometry pancreatitis depends on the rate and time of catheter perfusion and whether the pancreatic segment of the sphincter is evaluated[45]. Sherman *et al.*[46,47] have reported a reduction of procedure-related pancreatitis from 31 to 4 per cent following evaluation of the pancreatic segment of the sphincter when one lumen of the triple-lumen catheter was used to aspirate the intraductal juice continuously; there was essentially no change in the recording pressure caused by this modification.

In addition to the above, other problems confound the interpretation of manometric findings. Very few investigators have studied normal volunteers and even those who have have produced very small series. More accurate conclusions could be drawn from manometric data collected from large numbers of asymptomatic individuals over a wide range of ages, from both men and women, with and without cholecystectomy, fed and fasted, and observed over a long period of time[40]. On the other hand, many patients suspected of having sphincter of Oddi dysfunction have postcholecystectomy pain and the effect of gallbladder removal on sphincter activity has not been determined. Thus an important control group that should be studied in more detail is that containing asymptomatic subjects after cholecystectomy[2]. The test itself may be problematic in that a relatively large tube is placed in a small opening, leading to obstruction of the biliary system, which is then perfused with water at low pressure[40]; the patient is sedated. For these reasons the procedure does not reproduce normal physiological conditions[40]. Methodological variations in catheters and infusion systems may account for differences in absolute pressure measurements between different laboratories. The problem of interobserver variability in the interpretation of manometry data has been addressed recently and significant disagreement was found in the reading of the absolute basal sphincter pressure and in the final diagnosis of normal *versus* abnormal[48]. However, in one study from a centre with a large experience of endoscopic manometry, when three experienced observers reviewed randomly selected manometric tracings, agreement was reached in a high proportion of cases in evaluation of normal *versus* abnormal baseline sphincter pressures[49].

Another question which is difficult to answer is whether or not the abnormalities noted on sphincter manometry correlate with pain, because the patient is sedated during the procedure. Furthermore, the assessment of sphincter activity obtained by manometry is limited to a brief period and this may be misleading in view of the intermittent nature of the disorder[40]. Tanaka *et al.*[50] overcame this problem by using the tip transducer technique in which an indwelling microtransducer catheter is placed into the CBD at the time of ERCP and remains there after removal of the endoscope and recovery of the patient. This method has the advantages of being more physiological and permitting the collection of information over a longer period. It also allows the evaluation of the effect of agents, such as morphine or smoking, on sphincter motility, and the correlation of intensity of pain with changes in sphincter pressure.

It is estimated that, if endoscopic manometry were employed to screen patients with postcholecystectomy pain, 7·2 studies would be performed for every case of sphincter of Oddi dysfunction detected[28]. This efficacy ratio is unacceptable for an invasive procedure that is both difficult to perform and associated with potentially dangerous complications. Biliary manometry is an important method of evaluation of sphincter of Oddi function, but at present it is more useful as a research tool than as a routine clinical investigation.

For indirect biliary manometry a catheter is inserted into the cystic duct or a T tube, fluid infusion is performed and pressures are obtained. Tondelli and Gyr[6], in 1983, described their debimanometer and proposed pressure-controlled cholangiography for intraoperative diagnosis of sphincter dysfunction. Their criteria for stenosis were residual pressure in the CBD of more than 16 cm contrast medium, standard flow through the papilla at a constant pressure of 30 cm contrast medium below 14 ml/min, and no normalization of these values after the administration of cholecystokinin. This method played an important role in understanding sphincter physiology using indirect methods that measured pressure in the CBD and flow through the sphincter, rather than direct measurement of the sphincter pressure. Other drawbacks, compared with endoscopic manometry, were that it could only be used during surgery and that it was both less physiological and less precise[9].

The ideal test to diagnose sphincter of Oddi dysfunction has yet to be identified, but endoscopic manometry is considered the best available by several authors, despite its obvious problems. In a recent prospective study[51], the Milwaukee Biliary Group Classification correlated well with clinical outcome after endoscopic sphincterotomy in 33 patients. Sphincterotomy was performed on the basis of raised basal pressure measured manometrically, but manometric findings did not correlate with either the Milwaukee classification or clinical outcome in patients with suspected sphincter of Oddi dysfunction type II (20 patients) or III (13). This poor correlation between the Milwaukee classification and manometric findings has been reported previously by others[52]. In another recent prospective series, which included patients with biliary type II and III disease, various preoperative tests were compared with respect to the results of sphincterotomy carried out on the basis of manometrically proven raised basal pressure in 23 patients[53]. A positive morphine–neostigmine test, pain induced by the injection of contrast agent at ERCP and delayed drainage of contrast from the CBD were associated with a favourable clinical outcome from endoscopic sphincterotomy in 18, 17 and 14 of the 23 patients respectively. These results were not significantly different from those of pathological sphincter of Oddi manometry, which was associated with a favourable outcome in 19 patients[53].

On balance, a single approach to the problem seems unjustified. Diagnosis and therapy should be based on a range of preoperative tests and clinical presentation. The

Milwaukee classification, which combines clinical, biochemical, ultrasonographic and ERCP findings, has a significant role to play in the assessment of suspected sphincter of Oddi dysfunction. This classification seems to predict the outcome of a sphincter ablation procedure accurately[51]. Intervention is justified in patients with type I disease, the vast majority of whom will experience benefit from sphincter ablation. In type II, the indication for any intervention is questionable; in type III, surgical or endoscopic intervention may create more problems than it solves. Manometry is not necessary for type I, as most patients have a uniformly abnormal basal pressure. In type II, it may provide useful information and identify a subgroup that may benefit from treatment. Most patients with type III disease have normal pressures so that manometry is redundant. If manometry is normal or not available, a diagnosis and a decision about intervention may be based on the rigorous application of available diagnostic tests.

Treatment

Sphincter of Oddi dysfunction is uncommon and is not life-threatening, but patients who suffer from it are severely debilitated. To make a diagnosis of sphincter of Oddi dysfunction and accurately select patients for treatment is difficult. When selection is based on strict criteria, the result may still be poor. An explanation for this is that sphincter dysfunction, particularly in dyskinesia, may represent part of a generalized gastrointestinal motility disorder. Treatment directed to one part of the gastrointestinal tract in such circumstances cannot be expected to improve or cure all symptoms[5,54].

The objective of treating sphincter of Oddi dysfunction is to facilitate drainage of biliary and pancreatic secretion into the duodenum. Three methods have been described which may achieve this goal: pharmacological treatment, endoscopic treatment (sphincterotomy and/or stenting) and surgical treatment (sphincteroplasty and biliary–enteric drainage). The endoscopic and surgical approaches are the most widely used.

The pharmacological approach has been proposed as a reasonable initial step, especially for functional dyskinesia[55]. Indeed, there is increasing interest in evaluating smooth muscle relaxants, such as nitrates or calcium channel blockers, based on the theory that the pain of sphincter of Oddi dysfunction is probably due to constriction of the sphincter and dilatation of the ducts proximal to the obstruction[2]. Bar-Meir *et al.*[56] reported a single case of nitroglycerine improving the pain of a patient with suspected sphincter dysfunction, with relaxation of the sphincter measured endoscopically. A therapeutic role for nifedipine was suggested by Laslo and Sandor[57], who reported an excellent clinical response from nifedipine therapy in four, a good response in seven and poor response in three of 14 patients with sphincter of Oddi dysfunction. Guelrud *et al.*[58] showed that nifedipine affects sphincter motor activity in both normal volunteers and patients with dysfunction by decreasing the basal pressure. Intolerable side-effects, however, limit the usefulness of these agents[58]. Recently Khuroo *et al.*[55], in a prospective double-blind randomized trial of 28 patients with dysfunction, showed that oral nifedipine at the maximum tolerated dose relieved pain in 21, principally in those with raised basal pressure and predominantly antegrade sphincter of Oddi contractions. The authors recommend that a trial of calcium channel blockers or long-acting nitrates is justified in biliary dyskinesia, retaining the other treatment modalities for those who fail to respond.

Some investigators have proposed stenting of the sphincter of Oddi as a minimally invasive method of treatment. In a recent study, stenting was used in patients with suspected sphincter dysfunction but no increase in basal sphincter pressure, on the assumption that these patients might have intermittent spasm[59]. There was a poor symptomatic response associated with a high risk of stent-induced pancreatitis, suggesting that stenting cannot be recommended as a routine method of treatment.

It is impossible to answer definitively the question of whether or not endoscopic sphincterotomy is better than surgical sphincteroplasty; no randomized trial comparing these two treatments has been carried out and the results from either retrospective or prospective trials of either option contain inherent bias. Furthermore, the heterogeneous patient populations and the different selection criteria used in different series make results difficult to compare in any meaningful way. The results of both surgical and endoscopic series published in the past 15 years are presented in *Tables 3* and *4*. Poor results are common with both endoscopic sphincterotomy (13–39 per cent) and surgical sphincteroplasty (7–35 per cent). This probably reflects the lack of specific objective tests to diagnose the disorder accurately and to select patients for intervention.

As endoscopists have become more adept at sphincterotomy, treatment seems to have shifted from surgical to endoscopic methods[71]; still, there is no evidence in the literature to suggest superiority over surgical sphincteroplasty. According to some authorities[71], treatment should be modified depending on co-existing medical illness, secondary hepatic dysfunction, the degree of pain, periampullary anatomy, and the type and degree of sphincter dysmotility. In an important prospective study

Table 3 Results of surgical treatment

Reference	Year	*n*	Follow-up	Result	Morbidity (%)
Moody *et al.*[60]	1983	83	1–10 years	Good: 43%; fair: 33%; poor: 24%	21
Nardi *et al.*[61]	1983	89*	5–20 years	Pain free: 50%	—
Anderson *et al.*[62]	1985	28	67·5 months (mean)	Good: 79%; poor: 21%	—
Stephens and Burdrick[63]	1986	81	6 months	Pain free: 68%; fair: 25%; poor: 7%	7
Hastbacka *et al.*[64]	1986	22	—	Good: 59%; moderate: 23%; poor: 18%	18
Williamson[65]	1988	20	6–100 months	Pain free: 60%; improved: 25%; poor: 15%	20
Nussbaum *et al.*[66]	1989	29	22 months (mean)	Good: 62%; fair: 14%; poor: 24%	38
Kelly and Rowlands[67]	1996	20	9–80 months	Pain free: 55%; good: 10%; poor: 35%	10
Toouli *et al.*[68]	1996	26*	9–105 months	Pain free: 58%; mild: 31%; poor: 12%	8

*For recurrent acute pancreatitis exclusively

Table 4 Results of endoscopic treatment

Reference	Year	*n*	Follow-up	Result	Morbidity (%)
Riemann *et al.*[69]	1983	25	2–9 years	Pain free: 48%; improved: 32%; poor: 20%	—
Roberts-Thompson and Toouli[42]	1985	46	25 months (mean)	Pain free: 13%; improved: 48%; poor: 39%	5
Thatcher *et al.*[20]	1987	46	14·9 months (mean)	Pain free: 67%	16
Neoptolemos *et al.*[15]	1988	30	46 months (median)	Good: 63%; poor: 37%	25
Seifert[70]*	1988	127	—	Pain free: 55·1%; improved: 32·3%; poor: 12·6%	—
Geenen *et al.*[41]†	1989	47	1 year	Good: 43%; fair: 35%; poor: 22%	—
Bozkurt *et al.*[53]‡	1996	23	19 months (mean)	Pain free: 57%; improved: 26%; poor: 17%	22
Wehrmann *et al.*[51]‡	1996	33	2·5 years (median)	Improved: 60% (type II), 8% (type III)	—

*National study, collective data from 25 German centres; †prospective randomized trial, type II Milwaukee classification, sphincterotomy ($n = 23$) *versus* sham ($n = 24$); ‡prospective trial, type II and III Milwaukee classification, manometric criteria for sphincterotomy

by Geenen *et al.*[41], 47 patients with biliary-like pain (type II) were randomized to endoscopic sphincterotomy (23 patients) or sham procedure (24). Manometry was carried out, but not used as a criterion to determine therapy, and the manometric findings were correlated with the clinical outcome. After a 4-year follow-up, 17 of 18 patients with abnormal basal pressure (greater than 40 mmHg) had an improvement in their symptoms after sphincterotomy, compared with one of five after a sham procedure. Among those with normal basal pressure (less than 40 mmHg) only five of 12 had an improvement after sphincterotomy, compared with four of 12 after the sham procedure. In this study sphincterotomy did not afford any therapeutic benefit beyond its placebo effect when the sphincter pressure was normal, in patients with type II disorder.

Endoscopic sphincterotomy performed for papillary stenosis may be associated with a higher morbidity rate than sphincterotomy for calculi[70,72,73]. Patients undergoing endoscopic sphincterotomy for papillary stenosis are five times more likely to develop restenosis at the sphincterotomy site than those who have endoscopic sphincterotomy for calculi[70]. Riemann *et al.*[69] described recurrent stenosis in two of six patients subjected to endoscopic sphincterotomy for papillary stenosis, and Bozkurt *et al.*[53] needed to repeat sphincterotomy in three of 23 patients because of restenosis. In a multicentre study (German National Survey) of long-term results after endoscopic sphincterotomy for papillary stenosis, recurrent stenosis, defined by radiological findings, occurred in 12 per cent of 96 patients[70]. Isolated cases of relapsing pancreatitis after endoscopic sphincterotomy have been reported and have been attributed to subsequent scarring and progressive narrowing of the pancreatic duct orifice[74].

Transduodenal sphincteroplasty with transampullary septectomy (TDS-TAS) has been well standardized over the past two decades and is designed to provide adequate drainage of both bile and pancreatic juice from their respective ducts. Originally, the procedure included division of the entire length of the sphincter of Oddi, with suturing of the mucosa of the bile duct to the duodenal mucosa to prevent narrowing of the opening and extravasation of biliopancreatic secretion[75]. Later, involvement of the transampullary septum in the inflammatory and fibrotic process with subsequent obstruction of the pancreatic outflow was demonstrated by some authorities, who proposed the addition of septectomy to the original operation[31,60]. The same procedure carried out using a carbon dioxide laser has been proposed as a more rapid, accurate and safe method, with less haemorrhage and no greater complication rate than the classical surgical procedure[76].

There are two theoretical advantages of the surgical procedure over endoscopic sphincterotomy. First, endoscopic sphincterotomy does not affect the transampullary septum and drainage of pancreatic duct, although there are occasional reports of endoscopic septotomy[77,78]. The transampullary septum is considered to play a primary role in the pathological process because of the muscular interrelationships of the fibres of the sphincter. This thin veil of tissue is so strategically placed that, when thickened by inflammation or fibrosis, the outflow of bile or pancreatic juice may be compromised[60]. Indeed, studies have shown that separate recording from the pancreatic sphincter in patients with recurrent pancreatitis demonstrates manometric stenosis in the absence of the biliary sphincter[79,80]. There is strong evidence that pancreatic outflow obstruction is the cause of the severe episodic pain in some patients and they benefit from TDS-TAS. In the series of Moody *et al.*[26], 12 of 17 patients with previously unsuccessful but adequate sphincteroplasty obtained pain relief after excision of the septum. The second advantage of surgery over the endoscopic procedure is that a mucosa to mucosa apposition can be obtained. This is important in avoiding further scarring and restenosis of the ampulla[26,81].

It must be emphasized that in many surgical series there is a trend towards a better outcome when a procedure is performed for biliary rather than for pancreatic pathology[60,62,66]. The poorer results in the pancreatic group have been attributed to the presence of underlying parenchymal disease, even when that is not apparent by current imaging techniques[66]. A further distinction in the pancreatic group should be between acute recurrent and chronic pancreatitis, as the former has a significantly better outcome[63]. This is not surprising, in the latter, as the presence of established and radiologically documented parenchymal disease is likely to cause persistent symptoms even after an adequate drainage procedure. According to some authors, patients with chronic pancreatitis are not appropriate candidates for surgery, even when the stenosis is thought to be confined to the transampullary portion of the duct of Wirsung[26,66]. Invariably there are other sites of obstruction of the pancreatic duct proximal to the sphincter which are not appreciated either before or during operation, or there is significant underlying parenchymal disease[66]. In contrast, well selected patients with acute recurrent idiopathic pancreatitis may benefit from sphincteroplasty and septectomy, as has been reported recently by Toouli *et al.*[68]. These authors performed TDS-TAS on 26 patients with idiopathic recurrent pancreatitis strictly selected on the basis of abnormal manometric findings; they reported an excellent result in 15 and mild symptoms in eight patients. The poor results of earlier series are probably due to heterogeneous patient populations, and to inclusion of patients with alcoholic pancreatitis and narcotic dependence[68].

Conclusion

Sphincter of Oddi dysfunction is not a common condition, but it is a challenging one to diagnose and treat. Diagnosis and definition of the disorder often remain elusive or arbitrary. The high failure rate of endoscopic and surgical treatment reflects the difficulties in accurate diagnosis and the lack of specific objective criteria by which to select appropriate therapy. Furthermore, in a subgroup of patients, sphincter dysfunction is simply a part of a generalized gastrointestinal motility disorder; targeting the sphincter does not result in control of the symptoms. All procedures on the sphincter should be undertaken with caution after meticulous investigation, and patient selection should be based on strict objective criteria.

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Review

Recent advances in the surgical treatment of faecal incontinence

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Background Improved imaging and refined technology have led to a number of recent advances in the surgical treatment of faecal incontinence.

Methods Original articles, identified using a computer database (Medline), and recently published abstracts of meetings were selected on the basis of greatest clinical relevance; these were reviewed.

Results Ultrasonographic characterization has led to improved therapeutic strategies. Simple structural damage is readily identified and external sphincter repair results in a good outcome for a majority of patients. For more complex structural damage, or for the newly recognized primary internal sphincter degeneration, alternative treatment strategies are emerging. The electrically stimulated gracilis neosphincter and the artificial bowel sphincter offer good results. The latter may be a more simple operation. For structurally intact but weak sphincters, sacral nerve stimulation is a promising therapy. Other therapies, such as antegrade irrigation, may be helpful for patients with neurological disorders.

Conclusion Better imaging, refined classification and new operations are leading to improved surgical techniques for faecal incontinence.

What constitutes optimum surgical treatment of faecal incontinence is rapidly changing. This review examines the most important recent developments, many of which have been aided by improved imaging and refined technology. This is not a systematic review, as only preliminary results are available for many of the procedures cited. However, many of these treatments have demonstrated long-term efficacy in the management of urinary incontinence.

Most patients with faecal incontinence due to simple external anal sphincter structural defects benefit from overlapping sphincter repair[1,2]. The introduction of anal endosonography, with its ability to characterize internal and external sphincter structural damage, has greatly enhanced accurate selection of patients for repair[3]. When failure occurs it can be due to breakdown of the repair[3] or co-existent problems, such as irritable bowel syndrome. In patients with a single defect involving the external sphincter the treatment course is relatively clear. Less clear, however, are the best surgical options for those with weak but intact sphincter muscles, internal anal sphincter defects or complex external sphincter injuries. Some are helped by biofeedback and some by antidiarrhoeal drugs, such as codeine or loperamide, but these are not a satisfactory long-term solution for many.

New treatments are required for patients with intractable faecal incontinence who are not suitable for, or who have failed, simple repair, biofeedback and drug therapy. To avoid a colostomy it is often necessary to perform invasive or major surgery, which may be complex and without the success rates expected from simple repair. At present there is increasing interest in new surgical approaches to faecal incontinence, many of which appear to have encouraging early results. Anorectal physiology studies and endoanal ultrasonography should now be a standard part of preoperative assessment as outcome depends as much on the characterization of the underlying problem and correct choice of operation as it does on surgical technique. In complex cases endoanal magnetic resonance imaging (MRI) may add to information obtained from ultrasonography in defining the external sphincter[4].

Advances in diagnostic imaging of the anal sphincter

The introduction of endoanal ultrasonography in the 1980s radically altered the previously held view that pudendal nerve damage was the underlying cause of faecal incontinence in most patients[5]. Ninety per cent of those presenting with faecal incontinence, in whom the only apparent predisposing factor was childbirth, have detectable structural damage to the external sphincter, internal sphincter, or both[6]. Changes in pudendal nerve function were noted to co-exist with structural damage, the latter accounting for the muscle weakness and incontinence. Ultrasonography has not only defined structural damage to the sphincter complex but has also allowed the recognition of degenerative disorders of the sphincter muscles[7].

MRI using an endoanal coil is not an economically practical substitute for endoanal ultrasonography, but it does provide improved images of the external sphincter and of fistulous tracks. For those who have equivocal findings on ultrasonography or who need further definition of possible sepsis related to faecal incontinence, MRI is a major advance[8,9].

Simple structural defects

The commonest cause of a reparable defect in the anal sphincter muscles is obstetric trauma. Thirty per cent of women after their first vaginal delivery have structural damage to the anal sphincter mechanism which may be seen on endoanal ultrasonography[10] and this increases to 80 per cent following a forceps delivery[11,12]. In primi-

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parous women studied before and after delivery, both sphincter muscles were structurally affected in 13 per cent of cases, the external sphincter alone in 6 per cent and the internal sphincter alone in 16 per cent[13]. Isolated damage to the internal sphincter is considered to be due to shearing forces as opposed to direct tearing. The perceived high percentage of isolated internal sphincter injuries may change with improving definition of the external sphincter muscle by higher frequency ultrasonography and its excellent definition using endoanal MRI. Where there is a single defined defect involving the external sphincter alone or in combination with the internal sphincter, the operation of choice is overlapping sphincter repair[2,14]; this may be used successfully even in the delayed situation[3] and in the elderly[15]. A non-overlapping repair is employed in the acute situation by many obstetricians and it has been used with some success by surgeons in the non-acute situation[16]. Acute overlapping repair is now preferred by some gynaecologists[17]. In the absence of sepsis, single surgical or traumatic injury to the external or both sphincters can usually be treated in the same manner as obstetric injury, using an overlapping sphincter repair[18].

Weak but intact sphincters

Most patients with faecal incontinence were previously believed to have weak sphincter muscles due to progressive denervation[5,19]. With the advent of endosonography, most of these patients may been shown to have structural damage. In the remainder, primary degeneration and weakness of the internal anal sphincter smooth muscle[7] or weakness of the external striated muscle sphincter are the commonest findings. True isolated neuropathy appears to be rare.

Idiopathic incontinence

Postanal repair. A comparison of treatment modalities for idiopathic faecal incontinence must be preceded by a thorough assessment to exclude sphincter defects or abnormalities, and this must include endoanal ultrasonography[20]. Studies conducted before the availability of this imaging technique[21–23] did not give a totally accurate characterization of the pathology and are probably not as reliable as subsequent studies in which sphincter damage was excluded. As a result of the changed emphasis away from neurogenic injury, the physiological basis for postanal repair is now being questioned. Although short-term benefit occurs in up to 83 per cent of patients, long-term improvement may be present in as few as 28 per cent[24,25] with only 21 per cent fully continent[26]. The addition of internal sphincter plication to a pelvic floor repair confers no benefit and may damage the sphincter muscles, with a fall in mean resting pressure[27]. Total pelvic floor repair or the addition of an anterior levatoplasty and (possibly) external sphincter plication to a postanal repair may improve the results[23,28], but reports contain small patient numbers and short follow-up.

Sacral nerve stimulation. Alternative treatments are needed for patients with weak but intact sphincters. Intermittent direct electrical stimulation of the anal sphincters (via the anal canal) has a limited effect on sphincter function[29,30]. Continuous stimulation of the sacral nerves in the treatment of patients with bladder dysfunction has been used since 1981[31–37]. A recent report[38] describes its use for faecal incontinence in patients with a weak but intact external sphincter. Patients undergo a short trial of stimulation using percutaneous electrodes (usually placed through the S3 foramen) and an external stimulator. If there is symptomatic improvement over several days the patient proceeds to implantation of a permanent electrode and a stimulator, identical to that used for dynamic graciloplasty. The permanent implantation of the electrode is performed through an incision over the sacrum; the leads are tunnelled to the stimulator which is implanted in the anterior abdominal wall. Even after 26 years of experience with this technique in urological practice, the mechanism of action remains unclear, although it appears to alter sacral nerve reflexes rather than to change motor function directly.

In the only published study to date of the application of this technique to the anal sphincter. Matzel *et al.*[38] report a marked improvement in faecal incontinence and external sphincter pressures in three patients who received a permanent implant. Those who might benefit from such treatment, however, remain poorly defined. A detailed study of the short-term effects of sacral nerve stimulation[39] describes a moderate increase in median squeeze pressure with no effect on the resting pressure. Ambulatory studies show decreased rectal contractility and some qualitative changes in resting anal pressure activity. No consistent effect is noted in electrosensitivity or compliance. The increase in squeeze pressure may be secondary to stimulation of α motoneurones and the qualitative changes in ambulatory manometry due to a modulation of sacral nerve reflexes via stimulation of A-δ fibres.

Incontinence associated with specific disorders

Rectal prolapse. Rectal prolapse should be excluded in patients with sphincter weakness without an obvious structural defect. Endoanal ultrasonography can suggest this diagnosis by demonstrating an abnormally thick or thin internal sphincter muscle and subepithelial thickening. Faecal incontinence occurs in 30–80 per cent of patients with full-thickness rectal prolapse[40]. Internal sphincter function recovers after abdominal rectopexy, which may be the only intervention necessary to restore continence[41–44]. Madden *et al.*[42] found that 17 of 23 patients were continent for solid and liquid stool after rectopexy, compared with only eight before surgery. Delemarre *et al.*[44] also found 17 of 23 patients continent for solid and liquid stool after operation, compared with five before surgery. Improvement may be related to removal of the source of persistent rectoanal inhibition[45], or to the prolapse no longer holding the anus open[46,47]. Recovery of continence has also been documented after perineal surgery, such as Delorme's procedure; while the results are probably not as impressive as after rectopexy[48], some reports claim an improvement of up to 83 per cent[49]. Perineal rectosigmoidectomy with levatoplasty results in improvement in continence in 46 per cent[50] to 90 per cent[51] of patients. The technique of laparoscopic rectopexy should have the same effect on continence as its transabdominal predecessor, but no long-term results have yet been published. The management of incontinence persisting after prolapse repair remains difficult. Postanal repair after rectopexy is of limited value; one study describes improvement in seven of nine patients[52] but only two were continent to both solid and liquid stool.

Diabetes mellitus. Incontinent patients with diabetes mellitus have a combination of somatic neurogenic and autonomic dysfunction[53–55] which is not amenable to simple surgical procedures. The long-term benefit of therapies such as biofeedback and sacral nerve stimulation has yet to be determined.

Progressive systemic sclerosis (scleroderma). The most consistent anal lesion encountered in faecal incontinence secondary to systemic sclerosis is marked atrophy of the internal sphincter leading to passive leakage[56]. Constipation resulting from disordered colonic motility may sometimes mask the sphincter weakness. Some patients may also have altered rectal compliance, acquired megacolon or bacterial overgrowth, leading to diarrhoea and greater stress on the sphincter. There is no simple surgical solution for the anal lesion. Those affected also have a higher incidence of rectal prolapse[57].

Spinal injury and other neurological disorders. Faecal incontinence is present in a high proportion of patients with spinal injury[58]. This can be a particular problem after laxative use for constipation, as there is no external sphincter activity to oppose bowel contraction. Faecal incontinence also occurs in about 30 per cent of patients with multiple sclerosis[59]. In both disorders there is often a co-existent problem of constipation, which renders therapy more difficult.

Dynamic graciloplasty is contraindicated in any neurological disease that may involve atrophy of the gracilis muscle. In one report of 12 patients implanted with an artificial bowl sphincter, nine had faecal incontinence secondary to a neurological disorder[60]. These were a prolapsed intervertebral disc (three patients), polyneuropathy (two), benign spinal tumour (one), diabetic neuropathy (one), cerebral trauma (one) and myasthenia gravis (one). The short-term follow-up of these patients showed good results. Direct stimulation of the pudendal nerve is described by Schmidt *et al.*[61] in two incontinent patients with myelomeningocele. It is technically more demanding than sacral nerve stimulation and their long-term results seem disappointing (personal communication, R. A. Schmidt). In patients with intractable bowel problems due to spinal injury, formation of a colostomy can have a dramatic effect on quality of life[62].

Disrupted irreparable sphincters

Disruption of the anal sphincters not amenable to simple repair ranges from a single defect in the internal sphincter to total disruption of the anal sphincter with little or no residual muscle tissue. Internal sphincter defects are often due to common surgical procedures. Endoanal ultrasonography can demonstrate these after operations such as lateral sphincterotomy[63] and anal dilatation[64]. Increasing awareness of the extent and effect of sphincter damage that may be caused by such procedures, together with the availability of sphincter relaxing agents like glyceryl trinitrate ointment[65,66] or injected botulinum toxin[67], may reduce the incidence of this type of incontinence. Less avoidable surgical damage includes injury to the sphincter during the treatment of fistula. Extensive external anal sphincter damage may result from obstetric, surgical or other trauma; it may also follow unsuccessful surgery aimed at sphincter repair. A number of new treatments have been devised for disorders involving extensive or irreparable sphincter damage. Some may also have application in patients with profoundly weak but intact sphincters.

Collagen injection

When the patient has isolated passive leakage, drug therapy in the form of antidiarrhoeal agents is usually the best initial option. Repair of the internal sphincter muscle alone is not successful[68]. There is one report[69] of the use of collagen injection for internal sphincter insufficiency, but long-term results have yet to be established. This and other injectable materials have been used with some success in urinary incontinence[70,71].

Skeletal muscle transposition

When there is severe passive leakage from internal sphincter disruption, severe disruption of both sphincter muscles or failure of a previous repair, a surgical solution may involve replacement of the sphincter muscle with other striated muscle, implantation of an artificial material or the establishment of a colostomy.

The use of skeletal muscle wrapped around the anus to aid continence was first described by Pickrell *et al.*[72] in 1952; these authors used the gracilis muscle. Despite modifications, such as intermittent stimulation, the fast-twitch skeletal muscle could not attain the capacity for prolonged contraction. The procedure was, therefore, reliant to some extent on the muscle being wrapped tightly enough to cause some degree of obstruction. The results were poor[73,74] and the operation fell into disrepute. Other muscles which have also been used to encircle the anus include gluteus maximus[75–78] and obturator internus[79]. Patients may find the gluteus muscles easier to contract than the gracilis as the former are natural synergists of the anal sphincter[80]. However, there may be more of a functional deficit after transposition of the gluteus muscle than after graciloplasty, and the gluteus operation has not achieved better results than unstimulated graciloplasty[81], although the two operations have not been compared directly.

The use of muscle wraps was revived with the discovery that chronic stimulation of a skeletal muscle can convert fast-twitch, fatiguable muscle into slow-twitch, less fatiguable muscle. With chronic stimulation there is an increase in the number of capillaries, an increase in aerobic oxidative capacity and a decrease in muscle fibre diameter. The actual number of muscle fibres remains unchanged[82,83]. The first chronically stimulated graciloplasty was performed in 1986 by Baeten *et al.*[84] in Maastricht. This work, combined with that of Williams and colleagues in London[85], has led to the general acceptance of the 'dynamic graciloplasty' as a treatment option for severe faecal incontinence. Results and complications vary from centre to centre[86,87]. Most surgeons reserve it for patients in whom conventional treatments have been tried or are considered inappropriate. Contraindications to dynamic graciloplasty include perianal sepsis, thereby excluding patients with Crohn's disease. Although no known ill effects have been reported from an active stimulator during pregnancy, it is recommended that the stimulator be turned off. Implanted pacemakers and defibrillators may be subject to interference from the stimulator controlling devices, and so dynamic graciloplasty may not be compatible when these are present. There is, however, one report of a patient who had both a cardiac pacemaker and a magnet-controlled graciloplasty stimulator without problems[88].

Although devascularization of the muscle 4–6 weeks before the gracilis wrap has been recommended[89], this stratagem has been omitted with success[90]. The procedure involves two components which may be performed at one or two operations. The gracilis muscle is traced to its distal attachment to the tibia through a medial incision in the thigh and a separate small incision just below the knee. The tendon is detached at its insertion and the muscle delivered into the thigh wound. Incisions are made laterally on each side of the anus, or anterior and posterior to the anus. A tunnel is created around the anus by finger dissection to accommodate the muscle wrap through 360°. A further track is then created from the perianal tunnel to the top of the thigh incision. The gracilis is then passed to the anal tunnel, wrapped around the anus in a γ, α or ε configuration, and its tendon secured to the contralateral ischial tuberosity.

Implantation of the stimulator and its leads may then be performed at the same or at a later operation. The nerve to the gracilis is located at the top of the thigh using a hand-held nerve stimulator. The electrode may either be in the form of a cuff placed directly around the nerve or a wire placed adjacent to the nerve branches. A pocket is created for the stimulator in the anterior abdominal wall through a transverse incision. The leads are tunnelled from the muscle up to this pocket and attached to the stimulator. The activation of the stimulator is usually delayed 4–6 weeks to allow the muscle to become fixed in its new position and the wounds to heal.

A bilateral gracilis wrap may also be used, but this is usually confined to the creation of a perineal colostomy after abdominoperineal resection for cancer or after extensive perineal trauma. The muscles may be used separately, one to form a neosphincter and the other to form a sling to replace puborectalis[87,91]. Alternatively, they may be used together to encircle the anus, coming from either side, around the back of the perineal colostomy and being joined anteriorly. This latter method of reconstruction has been used with some limited success, even without stimulation[92].

After wound healing an 8-week muscle stimulation programme is commenced on an outpatient basis. The stimulation is gradually increased until continuous stimulation can be applied to the muscle, resulting in sustained contraction. For defaecation the patient must switch off the stimulator to allow the muscle to relax.

Good results are reported in up to 78 per cent of patients who have undergone dynamic graciloplasty with continence for both liquid and solid stool[84,88,92]. The commonest complications are technical problems with the muscle wrap and with muscle stimulation, perianal infection, infection of the stimulator and leads, and anorectal functional imbalance. Such functional imbalance may lead to incontinence or to difficulty with defaecation[93]. Difficulty with defaecation is particularly marked in those with a history of evacuatory problems and in those who have not used the muscles of defaecation over a long period of time. Postoperative re-education about anorectal coordination during defaecation may be helpful.

The technique of graciloplasty continues to evolve. Intramuscular rather than perineural placement of the electrodes can avoid unnecessary exposure of, and therefore damage to, the nerve. A hand-held patient programmer working by telemetry is now replacing the magnets used previously to turn the stimulator on and off. The number of adjustments and hence the number of outpatient visits to convert the muscle to a non-fatiguable state is also being reduced. It may be possible to use another stimulated muscle in the leg if the gracilis is found to be unsuitable, although this is rarely necessary. The neurovascular anatomy of the biceps femoris is compatible with electrical stimulation in 75 per cent of cases[94] but sartorius has an unsuitable neurological supply[95]. The gluteus maximus may be stimulated but it does not function as well as the stimulated gracilis and requires a higher voltage, resulting in a shortening of the lifespan of the stimulator battery.

Artificial bowel sphincter

Experience with the artificial bowel sphincter is in its infancy. The artificial urinary sphincter was introduced in 1972 and is reported to produce total or near-total urinary continence in over 75 per cent of patients and improvement in a further 15 per cent[96]. The urinary sphincter (AMS Sphincter 800; American Medical Systems, Minneapolis, Minnesota, USA) has been used for faecal incontinence, with good result[60,97,98]. In 1996 the artificial bowel sphincter, a version of the artificial urinary sphincter modified to take account of anal anatomy, was introduced. The cuff which surrounds and occludes the anal canal is available in 14 different sizes, including three different widths: a 2-cm (narrow) cuff, a 2·9-cm (standard) cuff and a 3·4-cm (wide) cuff, and cuff lengths ranging from 7 to 12 cm. A pressure-regulating balloon, implanted in the abdominal wall, holds 40 ml of filling fluid and is available in seven different pressure ranges: 51–60 up to 111–120 cmH_2O. The control pump, placed in the labia or scrotum, contains the valves and resistor needed to transfer fluid to and from the cuff. It also has a deactivation button which is used to render the system inactive during the healing phase after operation or when any transanal procedure is to be performed.

The operation is carried out through two incisions, one anterior to the anus and one running transversely in the lower abdomen. A tunnel is created for the cuff in a similar way as for the gracilis muscle wrap. To avoid the possibility of perianal discomfort or cuff erosion, the tunnel should be made high up against the inferior aspect of the levator muscles. A sizer is passed around the anus to allow the correct width and length of cuff to be selected; when the cuff has been placed in position, its tubing is passed up to the lower abdomen and the anal wound is then closed. The balloon and the pump are implanted through the abdominal incision positioned just above the inguinal ligament. The balloon rests immediately behind the rectus muscle and the pump is placed in the labia or scrotum. Aseptic technique and filling the device with the correct volume of fluid without air bubbles are probably the two most vital aspects of this otherwise straightforward operation.

The first results of the European trial of the new AMS artificial bowel sphincter should be available in 1998. There have already been three published studies of anal incontinence treated with the urinary sphincter and modified urinary sphincter, from Christiansen and

Lorentzen[60] (12 patients), Lehur *et al.*[97] (13 patients) and Wong *et al.*[98] (12 patients). The overall success rate was 73 per cent (27 of 37 patients), with 20 patients totally continent of stool at all times and seven with some loss of liquid stool only. The major complications were infection and mechanical failure, both of which occurred in eight of the 37 patients. Only one patient with previous irradiation and scarring had erosion of the device through the perineum. As for graciloplasty, tightening of the anal canal can result in difficulty with defaecation after the procedure.

Colostomy and antegrade irrigation

The option of a colostomy for intractable incontinence should be reserved for those not suitable for conventional surgery and should not be regarded as a treatment failure. For some patients it is the optimal treatment, allowing return to as near normal a lifestyle as possible. Almost a quarter of patients, however, are unable to come to terms with a stoma. Those whose quality of life was poor before operation can often regain a more positive outlook on life[99]. Further improvement of quality of life can often be achieved by stoma irrigation[100]. Irrigation is possible in about 80 per cent of patients receiving a colostomy for cancer and it has been shown to be safe and cost effective[100]. There is no reason why similar figures could not be attained by those whose colostomy is for faecal incontinence.

An alternative strategy for faecal incontinence involves the creation of a proximal colonic stoma through which irrigation is performed to keep the distal bowel empty. The antegrade continence enema has been used in children, especially those with a congenital disorder, via an appendicostomy[101–103]. If the appendix is not available then a tubularized caecal flap can be used[104]. Long-term problems include stenosis at the mucocutaneous junction, reflux of irrigation fluid into the ileum and loss of responsiveness to infused fluid. A valved conduit with skin flaps, using the sigmoid and/or the transverse colon, has also been used; the greatest success has occurred with the transverse colon conduit in adult patients[105,106].

Congenital defects

Faecal incontinence associated with congenital abnormalities is common. It may occur as part of the primary abnormality, or following corrective surgery. Fifty-seven per cent of patients have soiling following a posterior sagittal anorectoplasty for anorectal malformation[107]. Fifty-five per cent of patients with spina bifida soil regularly[108]. Thirty-five per cent of children who have had a Duhamel operation for Hirschsprung's disease are incontinent when assessed at age 4 years or older[109]. Twenty-seven per cent of patients operated on for a benign sacral teratoma in infancy have some faecal soiling[110]. Those with anorectal malformation who have had a pull-through operation should be assessed to determine whether the sphincter muscle surrounds the bowel, using ultrasonography, MRI or electromyographic studies. If the bowel has not been pulled down through the muscle a transposition may be the first choice of procedure before any consideration is given to reconstructive surgery. The hindgut is also commonly abnormal in these patients and requires evaluation.

The 70 per cent success rates reported for dynamic graciloplasty have not been equalled in the group of patients with congenital problems, such as imperforate anus, where this is often an accompanying sensory deficit. In these patients good results can be expected in only about 50 per cent[84]. In the pilot studies of implantation of an artificial bowel sphincter only six of 37 patients had congenital defects and one of the six had cerebral trauma as well[60]. All six appear to have had a good result in the short term.

Conclusion

Successful surgical treatment of faecal incontinence depends on the accurate characterization of the motor, sensory and anatomical integrity of the anal sphincter mechanism. In most cases this can be achieved with a combination of a detailed history, careful examination, anorectal physiological studies and endoanal ultrasonography. In the future, MRI may emerge as a further important means of defining sphincter anatomy. The simplest and most successful surgical procedure is the overlap repair and this should be used as a first option in all patients with a single defect of the external sphincter or of both the external and internal sphincter muscles. More complex procedures have a role in well defined circumstances. Colostomy still has a role when it is desirable to avoid complex surgery.

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Simple laparoscopic gastropexy as the initial treatment of paraoesophageal hiatal hernia

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Background Paraoesophageal hiatal hernia is relatively rare compared with sliding hernia but it is associated with serious complications. Its clinical management presents a major challenge since many patients are elderly and unfit for a formal repair. This paper describes a laparoscopic method aimed at reducing the complications of open repair.

Methods Thirteen patients treated for symptomatic paraoesophageal hernia were included in the study. Eleven patients successfully underwent a simple laparoscopic modification of the Boerema anterior gastropexy. Two patients required an open anterior gastropexy through a minilaparotomy because of incomplete reduction of the hernia. A five-puncture technique was used. The stomach and any other contents of the sac were reduced into the abdomen and the stomach was firmly fixed to the fascia of the anterior abdominal wall with GORE-TEX sutures tied extracorporeally.

Results There was one postoperative death due to spontaneous intrathoracic perforation of the posterior aspect of the stomach in an elderly woman with severe cardiac disease. There was no postoperative morbidity. Eight of the ten patients who went home following laparoscopic gastropexy have remained asymptomatic on follow-up. In three patients, two in the laparoscopic group and one in the open group, symptoms recurred.

Conclusion While anterior gastropexy has a significant incidence of recurrent herniation, the clinical results of this simple procedure in a high-risk population support its use as the initial surgical option.

Paraoesophageal hiatal hernia is an uncommon clinical problem accounting for 2–5 per cent of all hernias[1]. Unlike sliding hernia, it is associated with a high incidence of complications and these are often severe and sometimes fatal[2–4]. They include gastric volvulus, obstruction, strangulation with perforation and upper gastrointestinal haemorrhage. For this reason, most authorities agree that the treatment of choice is operative repair. However, the timing of repair and the suitability of the patient for surgery present difficult clinical decisions[3]. In practice, many of those with symptoms are elderly, unfit and a poor risk for formal surgical repair. It is often difficult to judge the relative risks of surgery and of leaving the condition to take its course. These considerations led to the use of a very simple laparoscopic gastropexy in an attempt to improve symptoms and reduce the risk of complications with minimal operative trauma.

Patients and methods

Patients

Thirteen consecutive patients (11 women, two men) presenting with symptomatic paraoesophageal hernia over a 2-year period were studied. Most came from an inner city environment, hence the high prevalence of severe cardiorespiratory disease. The median age was 67 (range 46–87) years. Only two patients were younger than 60 years. Two additional patients presented during this time, but were unsuitable for a laparoscopic operation because of associated intestinal obstruction in one and previous multiple upper abdominal operations in the other. Both underwent conventional open surgical repair.

Eleven patients presented with epigastric and retrosternal pain after meals. Six had dysphagia and only one had heartburn. Gastroscopy was performed in all cases. No patient had oesophagitis. Visualization of the stomach was difficult at endoscopy and the distal stomach could not be seen in six patients because of gastric volvulus. Barium meal examinations were performed in all cases, and demonstrated gastric volvulus in six patients and large paraoesophageal hernias in the remainder. Oesophageal manometry and 24-h oesophageal pH recording were performed in the single patient with heartburn, but no pathological acid reflux was demonstrated.

Surgical technique

General anaesthesia was used throughout. After creating a pneumoperitoneum, a five-puncture approach was used. Cannulas were placed at the umbilicus, the epigastrium, the right upper quadrant, the left upper quadrant and the left flank. In some cases the hernia reduced easily and the port in the left flank was omitted. The hernia was reduced using atraumatic grasping forceps. Two GORE-TEX (W. L. Gore, Woking, UK) sutures were passed through the anterior wall of the stomach and brought out through the port sites in the epigastrium and the left upper quadrant. The sutures were passed through the linea alba or the fascia of the anterior abdominal wall and tied extracorporeally. A small portion of the stomach was herniated into these port sites to ensure firm fixation. This is effectively a modification of the Boerema anterior gastropexy but with suturing of the anterior wall of the fundus rather than the lesser curve of the stomach in the classical Boerema operation. No nasogastric tubes or drains were used.

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Table 1 Patients and their co-morbidity

Patient no.	Age (years)	Sex	Co-morbidity
1	87	F	Severe angina
2	81	F	CCF
3	75	F	Hypertension
4	74	F	CCF
5	72	F	COAD
6	71	F	COAD
7	67	F	None
8	63	M	COAD
9	62	F	None
10	62	F	None
11	61	F	CCF
12	48	M	Lung cancer
13	46	F	COAD

CCF, congestive cardiac failure; COAD, chronic obstructive airway disease

Results

The status of ten of the 13 patients was American Society of Anesthesiologists grade 3. The associated co-morbidity is listed in *Table 1*.

Eleven patients had a laparoscopic gastropexy completed successfully. Operating time ranged from 25 to 45 min. Two procedures were converted to open minilaparotomy with anterior gastropexy because of incomplete reduction of the hernia. Another patient, who presented as an emergency, had an incomplete reduction, but was deemed unfit for open surgery. Laparoscopic gastropexy of the incompletely reduced stomach was performed, but the patient died 3 days later. Post-mortem examination showed an intrathoracic perforation of the posterior wall of the stomach through an area described by the pathologist as 'gastromalacia'. There were no postoperative complications in the remaining patients.

The most difficult part of the operation was reduction of the hernia. Once reduced it was easy to suture the stomach to the anterior abdominal wall. Oral fluids *ad libitum* were allowed on the first postoperative day and light diet on the second day.

Eight of the 11 patients who had a completely laparoscopic gastropexy have remained asymptomatic on follow-up (median 10 (range 3–24) months). In two patients symptoms have recurred (at 2 and 6 months). Both patients were relatively fit and active compared with the others in the series. One has required formal open repair with good results; the other does not have symptoms severe enough to merit further operation.

Of the two patients who required minilaparotomy, one has had a partial symptomatic recurrence, but is being managed conservatively because of cardiorespiratory insufficiency. The other remains well.

Discussion

The treatment of paraoesophageal hernia in this series presented a significant surgical challenge because of the associated co-morbidity and high operative risk. All of the patients presented with severe symptoms compelling action despite the operative risk. The laparoscopic approach was selected in an attempt to decrease the morbidity associated with upper midline laparotomy. There was only one death in a very unfit elderly patient. It could be argued that in this patient the operation should have been converted to an open procedure, but the patient was considered unlikely to have survived this. Morbidity was otherwise minimal. One patient had incipient respiratory failure and was orthopnoeic. She was miserable with intractable vomiting due to gastric obstruction. Following laparoscopic gastropexy she was completely relieved of the vomiting and returned to community care 5 days later.

Most paraoesophageal hernias are of the mixed type in which the cardia is displaced above the diaphragm. The herniated stomach commonly rotates around its longitudinal axis causing organoaxial volvulus. Less frequently rotation occurs around the transverse axis causing mesentericogastric obstruction which may lead to strangulation, perforation, ulceration and haemorrhage with disastrous consequences. The incidence of these complications has been reported to be as high as 30–45 per cent[2–4] and the mortality rate from emergency operations may be as high as 50 per cent[2].

Prompt repair is therefore desirable in symptomatic patients. In asymptomatic patients, paraoesophageal hernia may be diagnosed incidentally by finding a retrocardiac gas bubble on a chest radiograph. The value of surgery in this group is less clear, but most consider that surgery should be offered to avoid dangerous complications at a later stage.

The present series is similar to others[3] in having a high proportion of elderly patients. The associated co-morbidity led the authors to adopt a minimalist approach to surgery, in the belief that the value of laparoscopic gastropexy is that it is a relatively simple procedure with little or no tissue dissection and little postoperative pain. Provided the hernia contents are completely reduced, it is a safe procedure that is remarkably well tolerated. The recurrences have occurred in the fitter patients in the series and it is tempting to speculate that such a simple gastropexy cannot withstand vigorous activity. Laparoscopic gastropexy is now therefore reserved for those with poor cardiorespiratory status.

The results of simple laparoscopic gastropexy for paraoesophageal hernia in this series compare surprisingly well with those of other methods. There was no associated morbidity in this series compared with a reported morbidity rate of up to 25 per cent[5,6]. Furthermore, eight of 11 patients have complete relief of their obstructive symptoms. However, laparoscopic crural repair is tedious and difficult in patients with these large hernias. For this reason some surgeons have used mesh repair of the hiatus[7], but reservations exist about the use of prosthetic mesh around the oesophagus. Although the crura were not repaired, fixation of the stomach to the anterior abdominal wall effectively seals the hiatus. The presence of gastro-oesophageal reflux is variable in those with paraoesophageal hernia. The symptoms of paraoesophageal hernia in this series were related to obstruction or volvulus rather than reflux, and the primary aim was the correction of obstruction and prevention of further volvulus. This is similar to the experience of Ellis *et al.*[5] and Williamson *et al.*[8]. In patients in whom laparoscopic reduction is not possible, open reduction and gastropexy at minilaparotomy seems a good alternative.

While laparoscopic gastropexy has a significant incidence of recurrent herniation, the clinical results of this very simple procedure in a high-risk population support its use as the initial surgical option in those unfit for major surgery.

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Pancreatic cancer resection in elderly patients

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Background Pancreatic cancer resection is considered a high-risk procedure in patients aged 70 years or older.

Methods Some 398 patients with pancreatic adenocarcinoma, observed between 1990 and 1995, were reviewed. Operative outcome and survival of 33 patients aged 70 years or more were compared with findings in 85 younger patients who underwent resection.

Results Resectability was not significantly different between the elderly and younger patients; neither were mortality or overall morbidity. However, patients aged 70 years or more had more relaparotomies ($P < 0.01$) and more haemorrhagic complications ($P < 0.001$). Nutritional recovery after resection was satisfying even for elderly patients (body-weight gain and increase in serum albumin concentrations, $P < 0.05$). Univariate analysis showed a moderately poorer survival in the elderly ($P = 0.09$). Multivariate analysis demonstrated that tumour diameter, grading and Union Internacional Contra la Cancrum stage were independent prognostic factors, whereas age was not.

Conclusion Patients aged 70 years or more can benefit from pancreatic cancer resection similarly to younger patients.

Pancreatic cancer has an extremely unfavourable prognosis: it is the fifth commonest cause of cancer death[1] and less than 20 per cent of patients are alive 1 year after diagnosis[2]. Its incidence increases with age[3–7]; in Italy, the cumulative risk for the age group 0–74 years is more than twice that of the group aged 0–64 years, for both men and women[7]. As the size of the elderly population has increased rapidly in recent decades, patients aged more than 70 years with potentially resectable pancreatic cancer will be seen more and more often. The dramatic reduction in the rate of operative complications after major pancreatic surgery that has been reported recently in several selected centres[8–11] is probably driving surgeons to approach pancreatic cancer aggressively in elderly patients as well. However, the cost–efficacy of this treatment, in terms of complications and postoperative survival, has not been discussed extensively.

The aim of this study was to assess how advanced age influences the selection of patients for resection and how it affects the operative and long-term outcome of patients with pancreatic adenocarcinoma.

Patients and methods

Between 1990 and 1995, 398 patients with histologically confirmed pancreatic adenocarcinoma were treated at this hospital; 300 were seen in the Department of Surgery and a further 98 received palliation in non-surgical departments. Demographic, perioperative and pathological data were collected prospectively in the departmental pancreatic surgery database; for patients observed in non-surgical departments, medical charts were reviewed. Some 264 patients were younger than 70 years of age (range 31–69 years) and 134 were 70 years or older (range 70–96 years). In all, 118 patients (29·6 per cent) underwent pancreatic resection: 85 were younger than 70 (mean 57; range 31–69) years and 33 were 70 (mean 74; range 70–83) years or older. The selection of patients for resection was performed by the surgical staff based on the presence of distant metastases, advanced invasion of peripancreatic great vessels or poor general condition.

Pancreaticoduodenectomy was performed in 75 patients aged less than 70 years and in 24 of the older group; total pancreatectomy was performed in one and two patients respectively; the remaining patients underwent distal pancreatectomy.

Operative outcome of patients aged 70 years or more was compared with that of younger patients. Operative mortality was defined as death within 60 days from operation (no operation-related death was observed after this interval).

Postoperative recovery of nutritional parameters was considered as a measure of quality of life: body-weight, expressed as percentage of usual body-weight, and serum albumin concentration were recorded at discharge and 6 months after operation.

Only patients with ductal adenocarcinoma (98 patients) were considered for analysis of postoperative survival, to exclude different histological types that could have a different prognosis. The Union Internacional Contra la Cancrum (UICC) classification[12] was used to define tumour extent; tumour differentiation was determined according to the criteria of Klöppel *et al.*[13]; radicality of the operation was defined according to the UICC-R (residual tumour) classification[14]. Most patients received adjuvant therapy (intraoperative radiotherapy (IORT) as previously described[15], postoperative chemotherapy or radiotherapy); this variable was also considered in the survival analysis.

Statistical analysis was performed with BMDP (Los Angeles, California, USA) statistical software; χ^2, Fisher's exact, Mann–Whitney U and Student's t tests were used as appropriate. Survival curves were calculated according to the Kaplan–Meier method[16]. The log rank test was used to detect differences between curves. A Cox proportional hazards model was used for multivariate analysis of survival[17]. Differences were considered significant when $P < 0.05$. Operative mortality was excluded from the survival analysis.

Results

Resectability

The resectability rate in the group of patients younger than 70 years was 32 per cent, compared with 25 per cent in those aged 70 years or more ($P = 0.3$). Greater selection of patients for resection was observed starting from 80 years of age (resectability rate 11 per cent), whereas those aged 70–79 years had the same rate as younger

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patients (35 per cent). Poor general condition was the main determinant of the decrease in the resectability rate in patients aged 80 years or more; there was no significant difference in the finding of distant metastases or advanced local infiltration in the different age groups over 60 years (*Table 1*).

Operative results

The operative outcome of patients who underwent resection, for patients of 70 years or more and those less than 70 years, is shown in *Table 2*. Mortality rate and the rate of overall complications were not significantly different between the two groups; however, elderly patients had haemorrhagic complications more frequently than younger ones ($P<0{\cdot}001$) and they had a higher rate of reoperation ($P<0{\cdot}01$). Nevertheless, the postoperative stay and the amount of blood transfused were not significantly different between the two groups. The comparison of possible risk factors (associated disease, Karnofsky status, operative blood loss, operating time) between patients over 70 years with and without complications did not identify any significant predictor of complications.

Table 1 Contraindications for resection in patients with pancreatic adenocarcinoma aged 60 years or more

	Age group (years)		
	60–69	70–79	80 or more
Overall no. of patients	136 (100)	80 (100)	54 (100)
Non-resected patients	96 (71)	52 (65)	49 (91)
Distant metastases	48 (35)	22 (28)	16 (30)
Advanced local infiltration	46 (34)	24 (30)	20 (37)
Poor general condition	2 (1)	6 (8)	13* (24)

$^*P<0{\cdot}01$ *versus* 60–69 and 70–79 years (χ^2 test)

Table 2 Operative outcome of 118 patients undergoing pancreatic resection for adenocarcinoma over or under the age of 70 years

	Age < 70 years (*n* = 85)	Age ≥ 70 years (*n* = 33)	*P*¶
Death*	3 (4)	2 (6)	0·5
Morbidity*	28 (33)	13 (39)	0·5
Relaparotomy*	3 (4)	6 (18)	< 0·01
Minor complications*‡	27 (32)	11 (33)	0·9
Overall haemorrhagic complications*	3 (4)	9 (27)	< 0·001
Causes of death*			
Sepsis	2 (2)	0 (0)	1·0
Disseminated intravascular coagulation	1 (1)	1 (3)	0·5
Stroke and intestinal infarction (embolism)	0 (0)	1 (3)	0·3
Causes of morbidity*			
Intra-abdominal bleeding§	2 (2)	5 (15)	< 0·05
Delayed gastric emptying	7 (8)	4 (12)	0·5
Pancreatic fistula	9 (11)	2 (6)	0·4
Abscess	4 (5)	3 (9)	0·4
Wound infection	4 (5)	3 (9)	0·4
Gastrointestinal bleeding#	0 (0)	3 (9)	< 0·05
Other	7 (8)	6 (18)	0·1
Operative blood loss (ml)†	700 (744)	750 (866)	0·4
Homologous blood transfusion (ml)†	400 (972)	400 (1200)	0·5
Operating time (min)†	400 (412)	370 (402)	0·7
Postoperative stay (days)†	16·5 (19·7)	17·0 (23·1)	0·3

Values in parentheses are *percentages or †mean. ‡Not requiring relaparotomy; §documented by relaparotomy or defined as the need for transfusion of more than 2 units of blood with evidence of intra-abdominal bleeding; #requiring transfusion of 2 units of blood or more. ¶χ^2, Fisher's exact, Mann–Whitney *U* or Student's *t* test used as appropriate

Nutritional changes

Data were available for 28 patients aged 70 years or more and for 75 aged less than 70 years. A significant increase in body-weight and/or serum albumin concentration was observed in both groups 6 months after discharge. Mean body-weight recovery (percentage of usual body-weight) was 5 per cent for patients aged 70 years or more (87 per cent at discharge *versus* 92 per cent after 6 months, $P<0{\cdot}05$) and 5 per cent for younger patients (88 per cent at discharge *versus* 93 per cent after 6 months, $P<0{\cdot}01$). Mean serum albumin level at discharge was 34 g/l in the older group and 35 g/l in younger patients; after 6 months the values were 38 g/l ($P<0{\cdot}05$) and 39 g/l ($P<0{\cdot}01$) respectively.

Patients with ductal adenocarcinoma

Characteristics of the 98 patients with ductal adenocarcinoma are listed in *Table 3*. With respect to younger patients, those aged 70 years or older had more advanced

Table 3 Characteristics of 98 patients who underwent resection for pancreatic ductal adenocarcinoma over or under the age of 70 years

	Age < 70 years (*n* = 69)	Age ≥ 70 years (*n* = 29)	*P*
Stage			
I	19 (28)	5 (17)	
II	7 (10)	1 (3)	0·15†
III	43 (62)	23 (79)	
Differentiation			
Well	11 (16)	1 (3)	
Moderate	35 (51)	15 (52)	0·08†
Poor	23 (33)	13 (45)	
Lymph node involvement	43 (62)	23 (79)	0·09‡
Resection			
R_0 (radical)	37 (54)	17 (59)	
R_1 (microscopic residue)	16 (23)	3 (10)	0·3†
R_2 (macroscopic residue)	16 (23)	9 (31)	
Adjuvant therapy*	54 (78)	16 (55)	< 0·05‡
IORT	47 (68)	13 (45)	< 0·05‡
Chemotherapy	36 (52)	2 (7)	< 0·001‡
External radiotherapy	27 (39)	5 (17)	< 0·05‡
IORT with chemotherapy and radiotherapy	26 (38)	1 (3)	< 0·01‡
Mean (range) tumour diameter (cm)	3·0 (1·4–5·5)	3·8 (1·5–7·0)	< 0·01‡
Mean (range) no. of lymph nodes removed	18 (0–50)	13 (0–35)	0·08‡

Values in parentheses are percentages unless otherwise stated. *Intraoperative radiotherapy (IORT), 15–25 Gy; chemotherapy, two to six courses of 5-fluorouracil 1000 mg per m^2 per day for 5 days plus epirubicin 50 mg/m^2 on day 1; external radiotherapy, 30–45 Gy in 1·8-Gy fractions. †χ^2 test for trend; ‡χ^2 or Student's *t* test as appropriate tumour extent, as shown by tumour diameter ($P < 0\cdot01$) and lymph node involvement ($P = 0\cdot09$), and there was a trend towards poorer tumour differentiation ($P = 0\cdot08$). As regards therapeutic approach, elderly patients had a lower number of lymph nodes removed ($P = 0\cdot08$) and they received adjuvant therapy less frequently than younger patients ($P < 0\cdot05$).

Median survival was 16 (95 per cent confidence interval (c.i.) 14–19) months for patients younger than 70 years and 14 (95 per cent c.i. 8–14) months for older ones ($P = 0\cdot09$). The actuarial survival rate of younger patients at 1, 3 and 5 years was 67, 14 and 9 per cent respectively; for patients aged 70 years or older the survival rate at 1 and 3 years was 53 and 0 per cent.

The following factors were significant predictors of survival by univariate analysis: UICC stage ($P < 0\cdot01$), tumour diameter ($P < 0\cdot01$), histological grading ($P < 0\cdot001$), residual tumour ($P < 0\cdot05$) and the association of IORT with chemotherapy and radiotherapy ($P = 0\cdot05$). Invasion of lymph nodes ($P = 0\cdot14$) and the number of nodes removed ($P = 0\cdot5$) were not significant prognostic indicators. The multivariate analysis of survival, with covariates of age, UICC stage, tumour diameter, grading, residual tumour, lymph node involvement, number of removed nodes and association of IORT with chemotherapy and radiotherapy, indicated that UICC stage (relative risk (RR) 1·59, $P < 0\cdot05$), diameter greater than 3 cm (RR 2·21, $P < 0\cdot01$) and grade (RR 2·65, $P < 0\cdot01$) were independent prognostic factors, whereas the remaining parameters (including age) were not.

Discussion

Life expectancy for the elderly population is getting longer: according to the life tables of the Italian population, the life expectancy of a 70-year-old person is 11·6 years for men and 14·7 years for women; at 80 years the values are 6·4 years for men and 7·9 years for women[18]. Median postoperative survival of patients having a pancreatic cancer resection is 10–18 months[19–22]. It follows that life expectancy could not be a reason for the exclusion of elderly patients with pancreatic cancer from the only chance of cure, which is radical resection.

In the present patients there was no decrease of the resectability rate until the age of 70 years, with a 35 per cent rate of resection in the age group 70–79 years. However, beyond the age of 80 years, the resectability rate dropped to 11 per cent, owing to the poor general condition of these patients. The comparison between patients with and without complications failed to identify clinical factors predicting operative complications.

Until the early 1980s poor results after major pancreatic surgery in the elderly were reported, with mortality rates ranging from 20 to 41 per cent[23–25]. However, improvements in perioperative supportive care, jointly perhaps with a more accurate selection of patients, have overturned these results: operative mortality rates of 10 per cent[26], 9 per cent[27], 6 per cent[28] and even 0 per cent[11,29] have been reported in elderly patients undergoing pancreatic resection.

In the present patients aged 70 years or more the mortality rate was 6 per cent and did not significantly differ from that in younger patients (4 per cent). Also, complications were not significantly more frequent in the older group (39 *versus* 33 per cent). An unexpected finding was the higher rate of haemorrhagic events and reoperation in the elderly patients; however, these complications did not prolong the postoperative stay and the amount of blood transfused was not significantly different between the two groups. A more careful attitude in the elderly may have permitted earlier relaparotomy, with the aim of preventing more severe sequelae.

As well as the complication rate, postoperative quality of life must be considered in the surgical decision regarding pancreatic cancer treatment in the elderly. After operation a significant improvement in nutritional status was observed in both groups, reflecting postoperative well-being in these patients. This suggests that even elderly patients may have improved quality of life after resection of pancreatic cancer.

As expected[19–22], postoperative survival was generally poor in these patients, with a slightly worse survival in patients aged 70 years or more: median survival was 14 months in the elderly and 16 months in younger patients ($P = 0\cdot09$); furthermore, no patient aged over 70 years survived for more than 3 years. However, advanced age did not have an independent negative prognostic role: the survival difference seemed to be determined by a combination of a more aggressive tumour behaviour and a less aggressive therapeutic approach. Patients aged 70 years or older had a greater tumour diameter, a trend towards poorer differentiation and a higher rate of lymph node invasion; these factors are recognized indicators of survival after pancreatic cancer resection[20,21,30–32] and the present experience has confirmed the prognostic role of tumour diameter and grade. A less aggressive therapeutic approach in elderly patients was shown by the smaller number of lymph nodes removed per patient and by the limited number of patients of 70 years or more who received adjuvant therapy. In the authors' experience, the association of IORT with chemotherapy and radiotherapy had a favourable effect on survival. Even though this study was retrospective, and selection of patients for adjuvant therapy cannot be excluded, long-term outcome may have been influenced by a difference in adjunctive treatment between the two groups.

According to this experience, age alone is not a limiting factor for pancreatic cancer resection in patients aged 70 years or more; they can tolerate the operation similarly to younger patients, with a satisfying nutritional recovery and minor changes in postoperative survival.

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Survival following pancreaticoduodenectomy with resection of the superior mesenteric–portal vein confluence for adenocarcinoma of the pancreatic head

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Background The survival of patients who underwent pancreaticoduodenectomy with or without *en bloc* resection of the superior mesenteric–portal vein (SMPV) confluence for adenocarcinoma of the pancreatic head was compared.

Methods To be considered for surgery, patients were required to fulfil the following computed tomography criteria for resectability: (1) absence of extrapancreatic disease, (2) no evidence of tumour extension to the superior mesenteric artery (SMA) or coeliac axis, and (3) a patent SMPV confluence. Tumour adherence to the superior mesenteric vein (SMV) or SMPV confluence was assessed at operation and *en bloc* venous resection was performed when necessary to achieve complete tumour extirpation.

Results Seventy-five consecutive patients underwent pancreaticoduodenectomy, 44 without venous resection and 31 with *en bloc* resection of the SMPV confluence. There were no perioperative deaths in either group; late (more than 6 months) occlusion of the reconstructed SMPV confluence contributed to the death of two patients. Median survival in the 31 patients who required venous resection at the time of pancreaticoduodenectomy was 22 months, and that for the 44 control patients was 20 months ($P = 0{\cdot}25$).

Conclusion Patients with adenocarcinoma of the pancreatic head who require venous resection during pancreaticoduodenectomy for isolated tumour extension to the SMV or SMPV confluence (in the absence of tumour extension to the SMA or coeliac axis) have a duration of survival no different from that of patients who undergo standard pancreaticoduodenectomy. These data suggest that venous involvement is a function of tumour location rather than an indicator of aggressive tumour biology.

The management of tumour adherence to the lateral wall of the superior mesenteric vein (SMV) or superior mesenteric–portal vein (SMPV) confluence represents the most challenging technical aspect of pancreaticoduodenectomy. This finding, whether unexpected or suggested by preoperative imaging studies, is usually not visible until after pancreatic and gastric transection, a point in the operation at which the surgeon has committed to resection[1]. If tumour is left on the lateral wall of the SMV or SMPV confluence, local recurrence and short survival are to be expected. Recent data have clearly demonstrated that patients who undergo pancreaticoduodenectomy with a positive margin of resection[2–6] have a survival duration similar to that of patients who have locally advanced disease treated nonsurgically with 5-fluorouracil-based chemotherapy and radiation[7]. In contrast, the intraoperative finding of tumour adherence to the SMV or SMPV confluence can be managed by partial or segmental venous resection and reconstruction. However, this allows resection of all gross disease only when tumour adherence is limited to the SMV or SMPV confluence. If tumour extension into the retroperitoneum with encasement of the superior mesenteric artery (SMA) is found, the additional operative time and potential patient morbidity involved in a complicated venous resection and reconstruction are wasted.

Several studies have demonstrated three fundamental principles of vascular resection at the time of pancreaticoduodenectomy. (1) Tumour involvement of the proximal SMA or coeliac axis, in contrast to involvement of the SMPV confluence, usually includes extensive involvement of the mesenteric neural plexus, making it impossible to achieve a negative retroperitoneal margin of excision even with radical resection[8–10]. (2) In contrast to arterial resection, segmental resection of the SMV or SMPV confluence can be performed safely with no increase in perioperative morbidity or mortality rate compared with standard pancreaticoduodenectomy[11,12]. (3) Tumour involvement of the SMPV confluence in the absence of tumour extension to the proximal SMA or coeliac axis is not associated with histopathological variables predictive of a poor prognosis; tumour invasion of the SMV or SMPV confluence appears to be a function of tumour location rather than an indicator of biological aggressiveness[11].

Despite recent reports supporting the safety of venous resection at the time of pancreaticoduodenectomy[12,13], the overall poor prognosis of patients with pancreatic cancer and reports suggesting even shorter survival in patients who undergo venous resection[6,14] have convinced many

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surgeons that isolated involvement of the SMV or SMPV confluence is a contraindication to pancreaticoduodenectomy. In an attempt to prospectively study this controversy, the authors' previous report outlined the anatomical rationale for venous resection and its safety in carefully selected patients[11]. The present study compares the survival of patients who underwent pancreaticoduodenectomy with or without *en bloc* resection of the SMV or SMPV confluence for adenocarcinoma of the pancreatic head. Importantly, all patients underwent standardized preoperative imaging using state-of-the-art contrast-enhanced computed tomography (CT). In contrast to all previously published reports outside of Japan, prospective evaluation of the retroperitoneal margin of excision was performed in all resected specimens.

Patients and methods

Data on all patients who underwent pancreaticoduodenectomy for adenocarcinoma of the pancreatic head or uncinate process from June 1990 to August 1995 were recorded prospectively in the pancreatic tumour database. Standardized preoperative imaging and operative techniques were applied to all patients. Preoperative evaluation included physical examination, chest radiography and contrast-enhanced CT. Angiography and laparoscopy were used selectively. To be considered for operation, all patients were required to fulfil the following CT criteria for resectability[15]: (1) absence of extrapancreatic disease, (2) no evidence of tumour encasement of the SMA or coeliac axis as defined by the presence of a normal fat plane between the tumour and these arterial structures, and (3) a patent SMPV confluence. The study group comprised all patients who required resection (tangential or segmental) of the SMV or SMPV confluence during pancreaticoduodenectomy. The control group comprised all patients who underwent pancreaticoduodenectomy that did not require any type of venous resection or reconstruction. Patients who underwent pancreaticoduodenectomy for diagnoses other than ductal adenocarcinoma were excluded. Also excluded were all patients who underwent operations other than pancreaticoduodenectomy (i.e. total pancreatectomy or distal pancreatectomy).

The majority of patients received adjuvant chemotherapy and radiation therapy (chemoradiation). Radiation therapy was delivered with 18-MeV photons either before operation to a total dose of 50·4 Gy (standard fractionation) or 30·0 Gy (rapid fractionation), or after operation to a total dose of 50·4 Gy. Concurrent with either standard- or rapid-fractionation radiation therapy, 5-fluorouracil was given by continuous infusion at a dose of 300 mg per m^2 per day, 5 days per week, through a central venous catheter[16,17].

All operations were performed using a standardized technique[18]. Tumour adherence to the SMV or SMPV confluence was assessed during surgery, and venous resection was performed if the surgeon was unable to fully mobilize the SMPV confluence from the pancreatic head or uncinate process because of presumed tumour adherence. Reconstruction of the SMPV confluence was performed using one of four techniques. Patients requiring tangential resection of less than one-third of the circumference of the SMPV confluence underwent repair with an autologous saphenous vein patch. Patients requiring segmental resection of the SMV or SMPV confluence had reconstruction with either an autologous internal jugular vein interposition graft, a GORE-TEX interposition graft (W. L. Gore, Flagstaff, Arizona, USA), or with a primary anastomosis without interposition grafting. The majority of patients who underwent primary anastomosis without interposition grafting required splenic vein ligation and division. Inflow occlusion was performed routinely during the period of venous resection and reconstruction; systemic heparinization was used at the discretion of the operating surgeon. Following tumour resection and venous reconstruction, many patients received electron-beam intraoperative radiation therapy; 10 Gy was delivered to the bed of the resected pancreas in a dedicated radiation therapy–surgical suite, obviating patient relocation[19]. All patients who underwent venous resection were begun on aspirin within 24 h of surgery and were requested to take low-dose aspirin 80 mg daily indefinitely. For determining length of hospital stay, the day of surgery was counted as day 1.

For pathological analysis, the operative specimen was oriented and dissected by the surgeon and pathologist in a pathology suite in the operating room complex. The retroperitoneal margin was defined as the soft tissue margin directly adjacent to the proximal 3–4 cm of the SMA. The margin was evaluated by frozen-section microscopic examination of a 2–3-mm full-face (*en face*) section of the margin and interpreted as positive if tumour was seen on this section. Tumour size was calculated following surgical resection by measuring the greatest transverse diameter of the tumour. In patients who had received preoperative chemoradiation this was often difficult, and in some specimens gross tumour could not be demarcated from uninvolved pancreatic parenchyma. Beginning in late 1993, a standardized system for the pathological evaluation of the pancreaticoduodenectomy specimen was performed to include histology of the segment of resected vein to determine the presence or absence of tumour cell infiltration of the vein wall; infiltration was defined as the presence of neoplastic cells within the tunica adventitia and/or tunica media of the vein wall[20]. On completion of pathological analysis, all cases were reviewed by a single histopathologist (K.R.C.).

Following the completion of all treatment, patients were evaluated by physical examination, chest radiography and thin-section, contrast-enhanced CT every 3–4 months. The venous phase of the most recently obtained CT scan was used to assess SMPV patency in patients who underwent venous resection. The reconstructed SMPV confluence was judged to be patent if the shape, contour and enhancement of the vessel were uniform from the level of the hepatic hilum to the level of the tributaries of the SMV. The SMPV confluence was judged to be patent but stenotic if the vessel contour was irregular and enhancement visible, but not uniform, throughout the region of venous reconstruction. The SMPV confluence was considered occluded if the vein could not be visualized or thrombus could be identified in the region of venous reconstruction. When the SMV or SMPV confluence was occluded, enlarged venous tributaries were often present in the small bowel mesentery and the mesocolon. All scans were interpreted by a single diagnostic radiologist (C.C.).

Statistical comparisons between groups were by χ^2 analysis of two-way frequencies and Student's two-tailed t test of differences between means. Overall survival analysis was by Kaplan–Meier product-limit estimation, and comparison of overall survival rates between groups was performed using log rank analysis. $P < 0·05$ was considered statistically significant.

Results

Seventy-five consecutive patients with adenocarcinoma of pancreatic head origin underwent either pancreaticoduodenectomy (44) or pancreaticoduodenectomy with *en bloc* resection of the SMV or SMPV confluence (31). There were 42 men and 33 women with a median age of 65 (range 42–81) years. The two treatment groups were similar with respect to sex, age, number of patients who underwent reoperative pancreaticoduodenectomy following a non-therapeutic laparotomy before referral to this institution, and the number of patients who received chemoradiation either before or after pancreaticoduodenectomy (*Table 1*). A significantly larger proportion of patients in the control group (36 of 44) than in the venous resection group (14 of 31) received intraoperative radiation ($P < 0·01$), possibly because of an initial reluctance to utilize intraoperative radiation following reconstruction of the SMV or SMPV confluence.

Operative and pathological characteristics are listed in *Table 2*. There were no perioperative treatment-related deaths, and all patients were successfully discharged from the hospital after a median hospital stay of 16 days for those who underwent venous resection and 15 days for those in the control group. The need for venous resection was associated with a significant increase in operative blood loss ($P < 0·001$). Median tumour size was significantly larger in patients who underwent venous resection ($P = 0·02$). No patient was found to have a grossly positive retroperitoneal margin of excision, and there was no difference in the frequency of microscopically positive retroperitoneal margins between treatment groups. Following the adoption of a standardized pathological examination, the most recent 18 operative specimens from patients who required segmental venous resection were evaluated pathologically for histological evidence of tumour invasion of the wall of the SMV or SMPV[20]. Adenocarcinoma was found to invade the vein wall in 13 of 18 specimens. Neoplastic cells penetrated into or through the tunica media in 12 of 13 specimens and were confined to the tunica adventitia in only one specimen.

Table 1 Patient demographics

	No. of patients	
	Venous resection ($n = 31$)	Control ($n = 44$)
Sex		
Male	19 (61)	23 (52)
Female	12 (39)	21 (48)
Median age (years)	66	64
Reoperative pancreaticoduodenectomy		
Yes*	9 (29)	10 (23)
No	22 (71)	34 (77)
Adjuvant therapy		
Preoperative chemoradiation	22 (71)	24 (55)
Postoperative chemoradiation	6 (19)	14 (32)
No adjuvant therapy	3 (10)	6 (14)
Intraoperative radiation therapy		
Yes	14 (45)	36 (82)
No	17 (55)	8 (18)

Values in parentheses are percentages. *Patients who had undergone abdominal laparotomy for planned pancreatic resection before referral, excluding patients who had undergone recent abdominal or biliary surgery for reasons other than resection of a pancreatic head tumour and patients who had undergone minilaparotomy for biopsy alone

Table 2 Operative and pathological characteristics

Variable	Venous resection ($n = 31$)	Control ($n = 44$)	P
No. of perioperative deaths*	0	0	
Median operative blood loss (ml)	1700	900	$< 0·001$
Median tumour size (cm)	3·5	3·0	0·02
No. with microscopically positive retroperitoneal margin	4 (13)	7 (16)	0·72
No. with positive lymph nodes	13 (42)	23 (52)	0·38
Median hospital stay (days)	16	15	0·93

Values in parentheses are percentages. *In-hospital or within 30 days of surgery

In patients who underwent venous resection, left internal jugular vein interposition grafting was the preferred method of reconstruction (*Table 3*). The infrequent use of tangential excision with saphenous vein (patch) repair suggests that most patients had apparent tumour involvement of greater than one-third of the circumference of the vein wall. As demonstrated in *Table 3*, patency rates were quite high when autologous tissue was used for reconstruction. Of the 11 patients who underwent internal jugular vein interposition grafting, nine were evaluable for graft patency. Three of the nine patients are dead from disease (at 13, 13 and 24 months from diagnosis), and six are alive with follow-up ranging from 12 to 37 months; all grafts were patent on the most recent contrast-enhanced CT scans.

A total of seven patients were documented to have occlusion of the reconstructed SMV or SMPV confluence (*Table 3*). Local tumour recurrence as a cause of venous occlusion could not be documented by CT or autopsy in any of these patients. Occlusion of the SMV or SMPV confluence was asymptomatic in five patients but directly related to the cause of death in two patients (8 and 16 months following pancreaticoduodenectomy). Both of these patients developed intractable ascites (cytology negative) and nutritional depletion, and one required emergency splenectomy for upper gastrointestinal haemorrhage secondary to sinistral portal hypertension.

Table 3 Method of venous reconstruction and patency at last follow-up

		Status of SMPV confluence		
Method of reconstruction	Total no. of patients	Patent	Patent with probable stenosis	Occluded
Saphenous vein patch	4 (13)*	2	0	1
Primary end-to-end anastomosis with ligation and division of the splenic vein	8 (26)	3	2	3
Primary end-to-end anastomosis without ligation of the splenic vein	7 (23)	4	1	2
Internal jugular vein interposition graft	11 (35)*†	7	2	0
GORE-TEX interposition graft	1 (3)	0	0	1
Total	31	16 (57)	5 (18)	7 (25)

Values in parentheses are percentages. *Includes one patient who could not be evaluated because follow-up radiographic images (performed elsewhere) were inadequate for assessment of graft patency. †Includes one patient who could not be evaluated who died from gastrointestinal haemorrhage secondary to a presumed marginal ulcer before undergoing adequate follow-up radiographic imaging. SMPV, superior mesenteric–portal vein

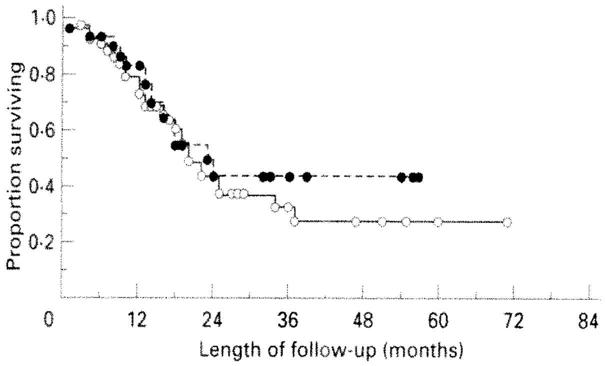

Fig. 1 Actuarial survival for 31 patients who underwent pancreaticoduodenectomy with venous resection (●) and 44 control patients who underwent standard pancreaticoduodenectomy (○). $P = 0{\cdot}25$ (log rank test)

Median follow-up was 17 months; minimum follow-up for all patients was 12 months. Overall median survival for the 75 patients was 21 months. Median survival in the 31 patients who required venous resection at the time of pancreaticoduodenectomy was 22 months and that for the 44 control patients was 20 months ($P = 0{\cdot}25$) (*Fig. 1*).

Discussion

The survival time of patients with adenocarcinoma of the pancreatic head who required *en bloc* resection of the SMV or SMPV confluence at the time of pancreaticoduodenectomy was no different from that of patients who underwent standard pancreaticoduodenectomy. This is consistent with the hypothesis that tumour adherence to or invasion of the SMPV confluence is a function of tumour location and possibly tumour size but not a prognostic factor associated with early tumour recurrence and short patient survival[11]. However, in contrast to previous reports on venous resection during pancreaticoduodenectomy, all patients in the present study underwent high-quality contrast-enhanced CT before tumour resection to ensure the presence of a normal fat plane between the tumour and the proximal SMA and coeliac axis origin. This vital tumour–vessel relationship must be assessed before operation. When assessed at the time of surgery, the relationship of the tumour to the proximal SMA can be examined directly only during the final step in tumour resection, following gastric and pancreatic transection. Furthermore, if the SMV or SMPV confluence is inseparable from the tumour, the proximal SMA cannot be accessed in the absence of interposition grafting (and medial retraction of the grafted SMPV confluence), or division of the splenic vein and lateral retraction of the specimen and attached SMPV confluence[1,21]. In either case, the surgeon has committed to venous resection and completion of pancreaticoduodenectomy even if tumour encasement of the SMA is found, in which case gross tumour will be left behind along the proximal SMA. A fundamental principle of venous resection at the time of pancreaticoduodenectomy is to operate only on patients who have no evidence of arterial involvement (*Fig. 2*). The Japanese experience with regional pancreatectomy clearly demonstrates that patients who have positive resection margins following even extended resection experience early tumour recurrence and short survival[22,23]. American and European data[2–6] also support a short survival time if tumour remains in the retroperitoneum along the proximal SMA following pancreaticoduodenectomy, regardless of whether a segment of SMV or portal vein was removed.

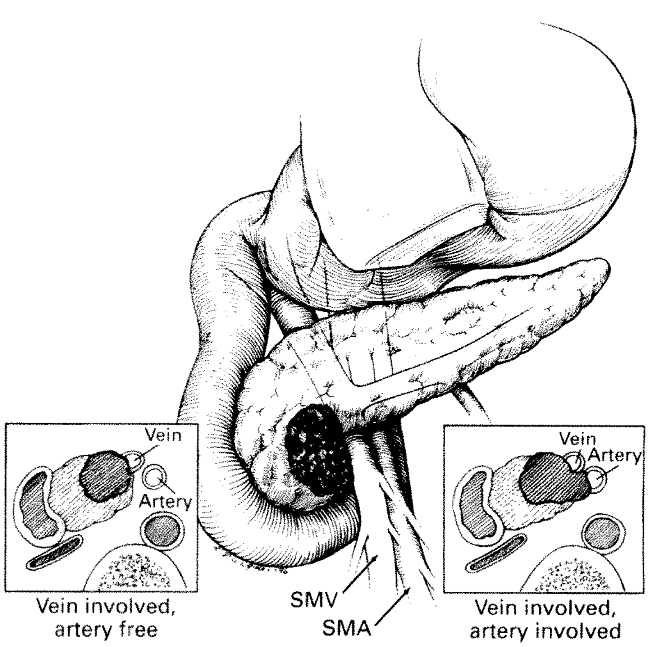

Fig. 2 Illustration of tumours in the pancreatic head involving the superior mesenteric vein (SMV) with and without invasion of the superior mesenteric artery (SMA). Attempted pancreaticoduodenectomy with resection of the SMV in the presence of tumour extension to the SMA will result in short patient survival; this is related to the surgeon's inability to achieve a negative retroperitoneal margin of resection and probably unrelated to whether or not a segment of SMV is removed

In the absence of information about prospective evaluation of the retroperitoneal margin (along the proximal SMA), reports of venous resection during pancreaticoduodenectomy are impossible to interpret. The lack of accurate evaluation of the retroperitoneal margin of resection and the high frequency of positive margins in patients who underwent venous resection (*Table 4*)[4,6,12–14,24–26] suggest that the majority of these patients had locally advanced tumours with arterial encasement and were poor candidates for pancreaticoduodenectomy. For example, Roder and colleagues[14] concluded that resection of the SMV or portal vein in patients with pancreatic adenocarcinoma was associated with a poor prognosis as demonstrated by a median survival of only 8 months. They concluded appropriately that their short patient survival was due to an incomplete resection (positive margin) in 15 of 22 patients. However, they provided no data to support the implication that the need for venous resection predicts margin positivity; that would be true only for patients with tumour extension to the proximal SMA, a finding that can be accurately assessed before operation with contrast-enhanced helical CT. Such patients should not undergo attempted pancreaticoduodenectomy; their locally advanced disease is currently best treated by chemoradiation, systemic gemcitabine or phase II investigational agents.

In this study, objective radiographic (CT) criteria were used for operation based on the belief that there is a fundamental difference between tumour involvement of

Table 4 Reports of venous resection during pancreaticoduodenectomy or total pancreatectomy (excluding the Japanese experience)

Reference	Year	No. of patients	Mortality rate (%)	Median survival (months)	Percentage with positive retro-peritoneal margin
Sindelar[26]	1989	20	20	12	n.a.
Trede *et al.*[4]	1990	12	0	n.a.	n.a.
Launois *et al.*[25]	1993	9	0	6·1*	n.a.
Allema *et al.*[24]	1994	20†	15	8	20‡
Yeo *et al.*[6]	1995	10	n.a.	n.a.§	n.a.
Fortner *et al.*[13]	1996	51	9	n.a.	—¶
Harrison *et al.*[12]	1996	50	6	13	24**
Roder *et al.*[14]	1996	22	0	8	68**
Current article	1997	31	0	22	13

*Mean; †Eight of 20 had adenocarcinoma of the distal bile duct or ampulla of Vater; ‡17 of 20 had positive resection margins overall; §3-year survival rate was 13 per cent; ¶patients with positive margins were excluded; **site of positive margin not defined. n.a., Data not available

the SMPV confluence and tumour involvement of the SMA[11]. The SMV is typically in direct contact with the pancreatic head and uncinate process and lacks an investing sheath of perivascular neural tissues. This allows direct extension to and invasion of the SMV or SMPV confluence by strategically located tumours even in the absence of tumour extension to the SMA. In contrast, the SMA lies posterior and medial to the SMV and is surrounded by the mesenteric neural plexus, a 2–4-mm investing sheath that extends laterally to the posterior aspect of the pancreatic head and uncinate process, and superiorly to the right and left coeliac ganglia[27]. Involvement of the SMA by a tumour in the pancreatic head or uncinate process defines locally advanced disease; the propensity for pancreatic adenocarcinoma to spread along perineural planes makes negative-margin resection unlikely in such cases even with arterial resection. Resection of the SMPV confluence should, therefore, be undertaken only in highly selected patients predicted to have venous but not arterial involvement based on preoperative contrast-enhanced CT. A high rate of negative-margin resections and the possibility of long-term survival may be anticipated only in this group.

Ishikawa and colleagues[28] recently published a system for angiographic typing of the degree of SMPV invasion by adenocarcinoma of the pancreas. They classified the contour of the SMPV confluence on the venous phase of the SMA angiogram based on the extent of presumed tumour invasion: type I, no invasion (normal venous phase); types II and III, abnormalities suggesting tumour invasion limited to the right lateral wall of the SMV or SMPV confluence; and types IV and V, bilateral invasion of the SMV or SMPV confluence. Patients with unilateral (semicircular) venous invasion (types I, II and III) had a 3-year survival rate of 59 per cent, whereas patients with bilateral venous invasion (types IV and V) all died within 18 months of pancreatectomy and had a median survival similar to that of patients who did not undergo pancreatic resection. Similar results were subsequently reported by Nakao and colleagues[29]. While these authors did not examine the retroperitoneal margin of resection as defined in this report, their results were exactly as one would predict based on the assumption that patients with angiograms demonstrating type IV or V disease probably had tumour extension to the SMA and probably underwent incomplete resections. A working knowledge of the three-dimensional anatomy of the SMA and SMV is critical for the pancreatic surgeon; tumours that extend to the left (medial) of the SMV on the venous phase of the SMA angiogram will virtually always involve the SMA. The proximity of the SMA to the posterior–medial aspect of the SMV is a constant anatomical finding easily seen on high-quality CT (*Fig. 3*).

In the present report, histological evidence of tumour invasion into the resected vein was seen in 13 of 18 specimens examined. This is in agreement with the findings of previous authors[23,30] and suggests that the surgeon's intraoperative assessment that venous resection is necessary to achieve complete tumour extirpation is correct in the majority of cases. Importantly, a previous report demonstrated that in 83 per cent of patients, contrast-enhanced CT correctly predicted the need for venous resection, as indicated by the presence of direct adherence of the low-density tumour to the lateral wall of the SMV or SMPV confluence[11].

The technical details of segmental resection of the SMPV confluence have been reviewed previously[18,21]. When tumour invasion of the SMPV confluence prevents mobilization and medial retraction of the SMPV confluence from the pancreatic head and uncinate process, access to the SMA origin and completion of the retroperitoneal dissection can be achieved in one of two ways: ligation and division of the splenic vein or venous resection and reconstruction. Division of the splenic vein at its junction with the SMPV confluence allows access to the origin of the SMA medial to the SMV and provides increased mobility of the portal vein, enabling a primary venous anastomosis to be constructed without tension[31]. However, splenic vein ligation occasionally results in gastrointestinal haemorrhage due to sinistral portal hypertension; one such case occurred in this study. Maintaining an intact splenic vein–portal vein junction has two important consequences in terms of surgical strategy. First, the intact splenic vein–portal vein junction significantly limits the mobilization of the portal vein and prevents primary anastomosis between the SMV and portal vein unless excision of the SMV is limited to less than 2 cm. Second, maintenance of an intact splenic vein prevents direct access to the proximal SMA, making completion of the retroperitoneal dissection impossible in most patients. This difficulty is circumvented by performing venous resection and reconstruction with autologous internal jugular vein before completion of the retroperitoneal dissection and removal of the specimen (*Fig. 4*). Placement of the interposition graft effectively restores a mobile length of SMV, which can then be retracted medially (to the patient's left), allowing retroperitoneal dissection along the origin of the SMA to be completed in the usual manner. Inflow occlusion during the time of venous resection and reconstruction is critical to prevent small bowel oedema.

In summary, these data suggest that venous resection during pancreaticoduodenectomy for adenocarcinoma of the pancreatic head is associated with a survival duration no different from that of patients who undergo standard pancreaticoduodenectomy. However, this conclusion is based on a programme of standardized preoperative imaging (staging) and operative technique. Future studies

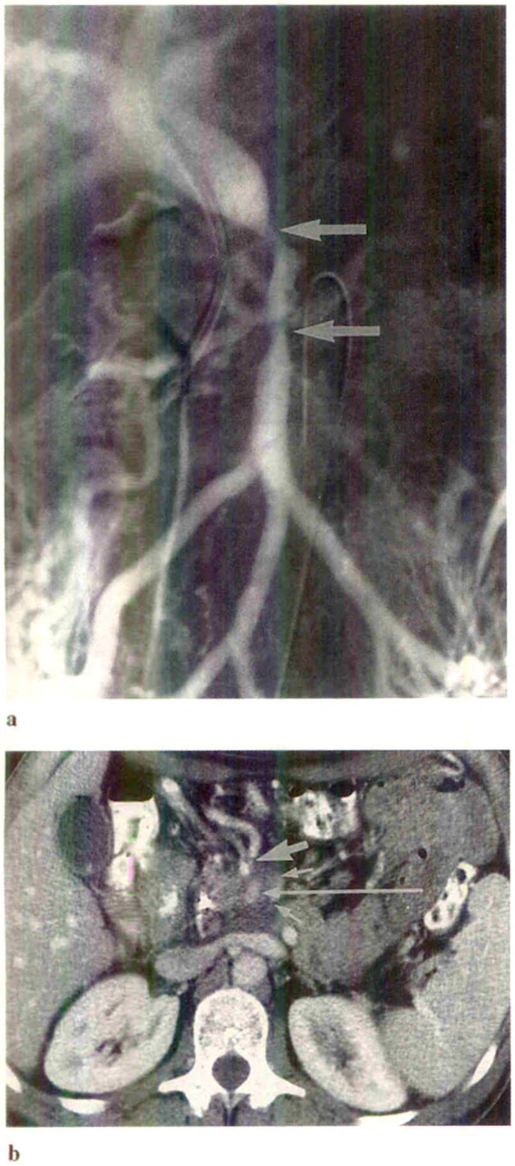

Fig. 3 **a** Venous phase of the superior mesenteric artery angiogram demonstrating bilateral narrowing of the superior mesenteric vein (SMV) (arrows). **b** Contrast-enhanced helical computed tomography in the same patient demonstrating tumour encasement (small arrows) of both the SMV (large arrow) and the superior mesenteric artery (long arrow). Bilateral narrowing of the SMV or superior mesenteric–portal vein confluence on angiography should always raise the possibility of tumour extension to the proximal superior mesenteric artery or coeliac axis. Note the dilatation of the middle colic vein due to significant narrowing of the SMV

examining this question must include similar objective criteria for operation combined with a standardized approach to pathological evaluation of the resected specimen.

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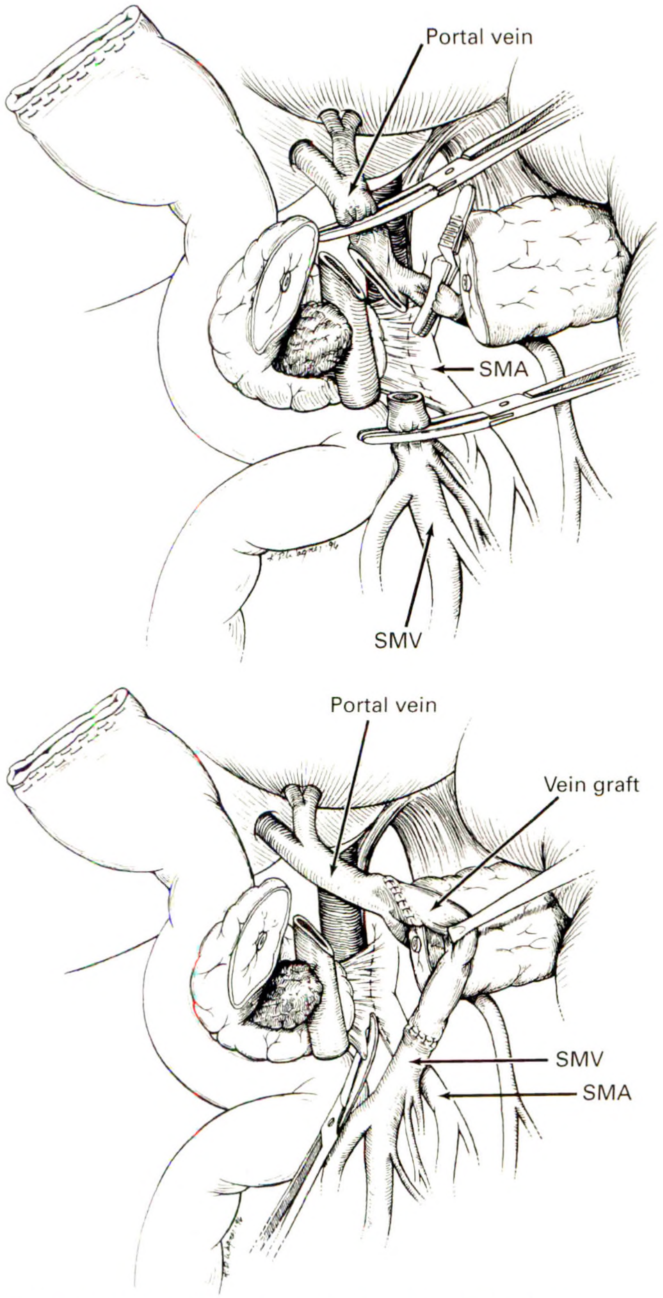

Fig. 4 Technique of venous resection and reconstruction. **a** Segmental resection of the superior mesenteric vein (SMV) is performed while the specimen is still attached to the superior mesenteric artery (SMA) before completion of the retroperitoneal dissection. **b** An internal jugular vein interposition graft enables medial retraction of the reconstructed superior mesenteric–portal vein confluence, allowing access to the retroperitoneum for standard dissection of the tumour from the lateral wall of the SMA

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Experimental study of a novel phospholipase A_2 inhibitor in acute pancreatitis

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Background In acute pancreatitis, two different types of secretory phospholipase A_2 (PLA_2) have been found: pancreatic type I PLA_2 and non-pancreatic type II PLA_2. In this study a potent new PLA_2 inhibitor effective against type II PLA_2 was used in an experimental model of acute pancreatitis.

Methods In 70 rats the efficacy of the compound was analysed in two experimental models of acute pancreatitis: cerulein- and taurocholate-induced acute pancreatitis, imitating mild and severe disease respectively. Serum rat type I PLA_2 protein concentration and type I and type II PLA_2 catalytic activities were measured while giving the inhibitor therapeutically. In a prophylactic protocol the effect on histology was analysed.

Results In the taurocholate model, type II PLA_2 activity was found to be nine-fold higher than in the cerulein model ($P < 0{\cdot}002$), whereas the activity of type I PLA_2 was not increased. The inhibitor significantly decreased serum type II PLA_2 activity in the taurocholate model of acute pancreatitis ($P < 0{\cdot}05$) but type I PLA_2 protein concentration and type I PLA_2 activity were not affected. The inhibitor also reduced histological tissue damage, with significant differences at 3 and 12 h ($P < 0{\cdot}01$).

Conclusion The PLA_2 inhibitor significantly reduced type II PLA_2 activity and was able to protect the pancreas against tissue damage. PLA_2 inhibition offers the possibility of a treatment for acute pancreatitis.

There is evidence that phospholipase A_2 (PLA_2) plays an important pathophysiological role in various inflammatory diseases, such as septic shock[1], adult respiratory distress syndrome[2], multiple injuries[3], diffuse peritonitis[4,5], and acute pancreatitis[6–8]. In human acute pancreatitis, highly significant increases in serum catalytic PLA_2 activity have been found which correlate well with the severity of the disease. However, measurement of pancreatic PLA_2 protein concentration has no prognostic value in acute pancreatitis, suggesting that there are two different types of PLA_2[6,8].

Meanwhile, two types of secretory PLA_2 have been identified: (1) the pancreatic type I PLA_2, with a disulphide bridge between cysteine at position 11 and cysteine at position 77, secreted by acinar cells; and (2) the non-pancreatic type II PLA_2, which lacks these cysteines and the corresponding disulphide bridge[9,10]. From human and experimental data it seems likely that type II PLA_2 plays the major pathophysiological role in acute pancreatitis[8,11].

With regard to a specific medical treatment for acute pancreatitis, various therapeutic approaches and innovative new agents have thus far proven ineffective[12,13]. The objective of this study was to examine the efficacy of a new low molecular weight PLA_2 inhibitor in two different experimental models of acute pancreatitis, simulating mild (oedema) and severe (necrosis) courses of the disease. Two questions were raised: first, whether effective inhibition of serum type II PLA_2 activity *in vivo* can be achieved and second, whether the inhibitor affects tissue damage in the pancreas.

Materials and methods

Seventy female Wistar rats, weighing 260–320 g, were used for the study. Approval for the experiments was obtained from the Animal Ethics Committee of the University of Bern.

Serum and tissue enzymes in cerulein-induced acute pancreatitis

The model of supramaximal stimulation of exocrine pancreatic secretion by the secretagogue cerulein (Takus; Farmitalia Carlo Erba, Bremen, Germany) in a dose of 5 μg per kg body-weight per h with a rate of 0·6 ml/h for 2 h was used to induce mild acute pancreatitis[14]. Immediately before cerulein administration, and at 3, 6 and 12 h after beginning of infusion, blood was taken via an implanted central venous catheter. The PLA_2 inhibitor was given intravenously 10 min (16 mg per kg body-weight) and 4 h (8 mg per kg body-weight) after the end of cerulein infusion. Twenty animals were used in this experiment: ten were untreated and ten were treated with the inhibitor. Rats without the inhibitor received an equal amount of 0·9 per cent sodium chloride solution.

After 12 h the whole pancreas was removed and immediately frozen in liquid nitrogen. After homogenization, lyophilization, dilution and centrifugation at 22 000 r.p.m. for 1 h at 4°C, PLA_2 enzyme concentration and activities were determined in the supernatants.

Serum and tissue enzymes in sodium taurocholate-induced acute pancreatitis

This experimental group also consisted of 20 animals: ten with the PLA_2 inhibitor and ten without. In these rats, acinar cell

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damage of necrotizing acute pancreatitis was induced by pressure-controlled (30 cmH$_2$O) intraductal injection of 3 per cent sodium taurocholate solution (Sigma, St Louis, Missouri, USA) in a dose of 0·1 ml per 100 g body-weight. Details have been given elsewhere[11,15]. The inhibitor was given intravenously 10 min (16 mg per body-weight) and 6 and 12 h (9 mg per kg body-weight) after the induction of acute pancreatitis. Blood samples were taken before the induction of acute pancreatitis and at 3, 6, 12, 18 and 24 h afterwards via an implanted central venous line. Animals not receiving the inhibitor were given an equal amount of 0·9 per cent sodium chloride solution. After 24 h the whole pancreas was removed and treated as in cerulein-induced acute pancreatitis.

Biochemical analysis of serum and pancreatic tissue

Rat pancreatic or type I PLA$_2$ protein concentration in its active or inactive form was measured with a time-resolved fluoroimmunoassay. The assay has been described in detail elsewhere[16]. The lowest type I PLA$_2$ protein concentration measurable with the assay is 0·25 ng/ml.

Measurement of lipase activity was performed with a commercially available enzymatic test kit (Monotest 10 Lipase, Boehringer Mannheim, Germany) adapted to the Hitachi 717 (Beckmann, München, Germany). The principle of the method has been given in detail elsewhere[17].

The total catalytic PLA$_2$ activity and type I and type II PLA$_2$ activities were measured with an *Escherichia coli* assay, based on the hydrolysis of phospholipids from [1-^{14}C]oleic acid-labelled *E. coli* membranes in the sn-2 position. Details of this bioassay are given elsewhere[18]. Differentiation into type I PLA$_2$ and type II PLA$_2$ activity was done using the different physiological properties of these enzymes. In contrast to type II PLA$_2$, type I PLA$_2$ is heat-stable at 60°C for 1 h[18,19]. Therefore, the heat-stable type I PLA$_2$ activity was measured in samples after heat treatment by the *E. coli* method, and type II PLA$_2$ activity was calculated by subtraction of type I PLA$_2$ from total PLA$_2$ activity (type II PLA$_2$ = total PLA$_2$ − type I PLA$_2$)[11,20].

Histomorphology in sodium taurocholate-induced acute pancreatitis

Thirty animals were used for histological assessment of the pancreas: 15 untreated and 15 treated with the inhibitor. Each of these groups was divided into three subgroups of five animals each. The inhibitor was given intravenously 10 min (32 mg per kg body-weight) before the induction of taurocholate acute pancreatitis and afterwards at 1·5 h (8 mg per kg body-weight) and 6 h (16 mg per kg body-weight). After either 15 min, 3 h or 12 h, the whole pancreas was removed, fixed in formalin and subdivided into four pancreatic segments (duodenal, biliary, gastric and lienal). The formalin-fixed tissue was embedded in paraffin, cut into 5-mm thick sections, and stained with haematoxylin and eosin. Histological findings were analysed using the method developed by Spormann *et al.*[21].

Characteristics of the phospholipase A$_2$ inhibitor

In vitro experiments with the new low molecular weight PLA$_2$ inhibitor (341·83 Da; BM 16.2056; Boehringer Mannheim) showed inhibitory capacities of 86 per cent against type I PLA$_2$ and of 100 per cent against type II PLA$_2$. The carrageenin–oedema model in the rat revealed marked anti-inflammatory effects at doses of 10–40 mg per kg body-weight per day[22,23]. Therefore, the above-mentioned dosages were used and repeated based on the fact that the PLA$_2$ inhibitor has been found to have a short serum half-life of approximately 10 min.

Statistical analysis

As the data were not distributed normally, all results are given as medians with lower and upper quartiles. Statistical differences between the groups were tested with the Wilcoxon test for paired and unpaired samples. $P < 0·05$ was considered statistically significant.

Results

Serum type I phospholipase A$_2$ protein concentration and lipase activity

In cerulein-induced acute pancreatitis the median peaks of type I PLA$_2$ protein concentration and lipase activity in untreated animals at 3 h were higher than in taurocholate-induced acute pancreatitis (type I PLA$_2$: cerulein 3355 ng/ml *versus* taurocholate 666 ng/ml, $P < 0·002$; lipase activity: cerulein 4540 units/l *versus* taurocholate 3020 units/l, P not significant) (*Table 1*). In both models no differences in the median levels of type I PLA$_2$ protein concentration and lipase activity were found for animals whether or not they were treated with the PLA$_2$ inhibitor, indicating that this compound did not interfere with the systemic uptake and/or synthesis of these enzymes.

Serum total phospholipase A$_2$ activity, type I and type II phospholipase A$_2$ activity

In untreated rats, median total PLA$_2$ activity at 3 h was significantly raised in taurocholate-induced acute pancreatitis (total PLA$_2$ activity: cerulein 7·2 units/l *versus* taurocholate 32·4 units/l, $P < 0·002$) (*Figs 1* and *2*). In cerulein-induced acute pancreatitis the increase in total PLA$_2$ activity was due to the increase in type I PLA$_2$ activity, whereas type II PLA$_2$ activity was found to be

Table 1 Serum type I phospholipase A$_2$ protein concentration and lipase activity in cerulein- and taurocholate-induced acute pancreatitis with (+) and without (−) the phospholipase A$_2$ inhibitor

	Time (h)					
	0	3	6	12	18	24
Type I PLA$_2$ protein concentration (ng/ml)						
Cerulein (−)	20 (20–23)	3355 (2921–3535)	305 (180–536)	54 (42–78)	—	
Cerulein (+)	18 (14–23)	3355 (2475–3658)	494 (442–643)	67 (56–83)	—	—
Taurocholate (−)	22 (19–24)	666 (568–744)	187 (181–199)	137 (89–142)	58 (35–72)	35 (28–37)
Taurocholate (+)	18 (15–22)	666 (565–753)	167 (155–303)	148 (62–206)	70 (24–30)	27 (24–30)
Lipase activity (units/l)						
Cerulein (−)	80 (40–100)	4540 (4165–5675)	3280 (1975–4235)	1350 (710–1520)	—	—
Cerulein (+)	60 (40–110)	4610 (3347–6340)	2920 (2580–3320)	1600 (1310–1715)	—	—
Taurocholate (−)	50 (40–65)	3020 (2145–4110)	1210 (960–1560)	470 (385–950)	200 (170–305)	120 (75–150)
Taurocholate (+)	40 (25–55)	2970 (2600–4030)	1590 (920–1975)	760 (455–1027)	390 (185–720)	200 (130–525)

Values are median with lower and upper quartiles. PLA$_2$, phospholipase A$_2$

unchanged (*Table 2*). In contrast to the cerulein model, median type I PLA_2 activity after 3 h was only slightly increased in taurocholate-induced acute pancreatitis, whereas type II PLA_2 activity was found to be increased nine-fold (type I PLA_2 activity: cerulein 4·5 units/l *versus* taurocholate 0·9 units/l, $P<0·002$; type II PLA_2 activity: 3·5 *versus* 31·1 units/l respectively, $P<0·002$).

Some 3 h after application of the PLA_2 inhibitor, a significant inhibition of total PLA_2 activity was found in cerulein-induced acute pancreatitis ($P<0·05$) (*Fig. 1*). Differential analysis of the two types of PLA_2 activity in cerulein-induced acute pancreatitis showed that the significant difference between the groups receiving and not receiving the inhibitor was caused by inhibition of type II PLA_2. In this mild model of acute pancreatitis, no inhibition of type I PLA_2 activity was demonstrated. In taurocholate-induced acute pancreatitis, total and type II PLA_2 activity were significantly inhibited through the application of the PLA_2 inhibitor at 3 h ($P<0·002$), 6 h ($P<0·002$), 12 h ($P<0·05$) and 18 h ($P<0·01$) (*Fig. 2*). As in cerulein-induced acute pancreatitis, type I PLA_2 activity was not inhibited in this severe model of acute pancreatitis.

Tissue enzyme analysis

In the removed rat pancreas with cerulein-induced acute pancreatitis, there were significant increases in type I PLA_2 protein concentrations and type I PLA_2 activity after 12 h in comparison with normal pancreatic tissue, whereas type II PLA_2 activity remained unchanged (type I PLA_2 protein concentration: normal pancreas 500 ng/mg *versus* cerulein 1120 ng/mg, $P<0·05$; type I PLA_2 activity: normal pancreas 0·8 units/g *versus* cerulein 23 units/g, $P<0·002$; type II PLA_2: normal pancreas 36 units/g *versus* cerulein 40 units/g, P not significant). In this mild model of acute pancreatitis no differences were found between animals with or without the PLA_2 inhibitor (*Fig. 3a*).

In the pancreas of rats with taurocholate-induced acute pancreatitis, however, differences were seen between animals with and without the inhibitor. Without the inhibitor, type I PLA_2 protein concentration and type I and type II PLA_2 activity were significantly reduced in comparison with the normal pancreas after the 24-h observation period (type I PLA_2 protein concentration: normal pancreas 500 ng/mg *versus* taurocholate 308 ng/mg, $P<0·002$; type I PLA_2 activity: normal pancreas 0·8 units/g *versus* taurocholate 0·1 units/g, $P<0·002$; type II PLA_2 activity: normal 36 units/g *versus* taurocholate 15 units/g,

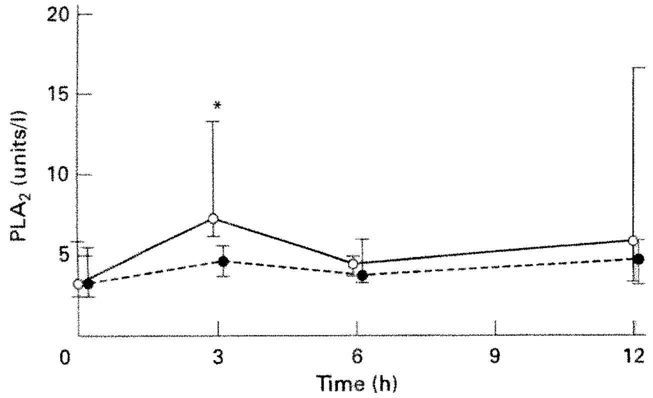

Fig. 1 Serum total phospholipase A_2 (PLA_2) activity in animals treated with (●) and without (○) the PLA_2 inhibitor in cerulein-induced pancreatitis. Values are median with lower and upper quartiles. $^*P<0·05$ *versus* no inhibitor (Wilcoxon test)

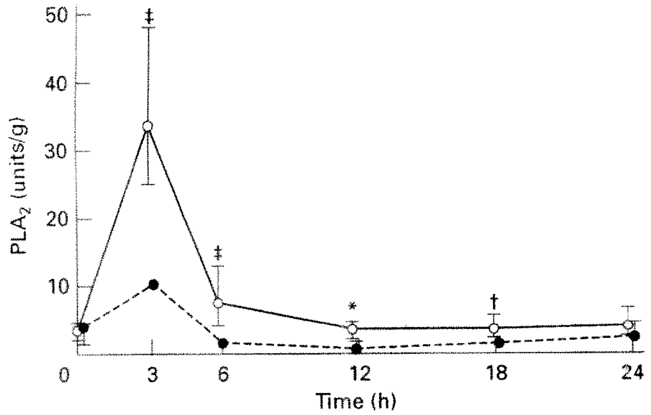

Fig. 2 Serum total phospholipase A_2 (PLA_2) activity in animals treated with (●) and without (○) the PLA_2 inhibitor in sodium taurocholate-induced pancreatitis. Values are median with lower and upper quartiles. $^*P<0·05$, $^†P<0·01$, $^‡P<0·002$ *versus* no inhibitor (Wilcoxon test)

Table 2 Serum type I and type II phospholipase A_2 activities in cerulein- and taurocholate-induced acute pancreatitis with (+) and without (−) the phospholipase A_2 inhibitor

	Time (h)					
	0	3	6	12	18	24
Type I PLA_2 activity (units/l)						
Cerulein (−)	0 (0–0·6)	4·5 (3·5–5·8)	0·4 (0·1–1·6)	0·5 (0·2–0·8)	—	—
Cerulein (+)	0 (0–0·6)	3·2 (2·7–3·6)	0·5 (0·1–0·7)	0·5 (0·3–0·7)	—	—
Taurocholate (−)	0	0·9 (0·7–1·0)	0·7 (0–1·2)	0·5 (0–1·0)	0 (0–0·4)	0
Taurocholate (+)	0	0·4 (0·4–2·5)	0·1 (0–0·5)	0 (0–0·8)	0	0
Type II PLA_2 activity (units/l)						
Cerulein (−)	3·2 (2·5–4·9)	3·5 (2·6–7·4)	3·6 (2·7–4·2)	5·2 (2·7–6·1)	—	—
Cerulein (+)	3·1 (2·5–5·4)	1·2 (0·8–2·4)*	3·4 (3·1–5·2)	4·4 (2·5–5·5)	—	
Taurocholate (−)	3·2 (2·0–3·4)	31·1 (29·6–34·1)	6·0 (4·2–8·1)	3·5 (1·1–3·9)	3·3 (2·1–5·4)	3·8 (2·8–6·5)
Taurocholate (+)	3·8 (1·5–4·5)	8·3 (7·7–9·9)§	1·5 (1·2–1·8)§	0·8 (0·3–4·1)†	1·4 (0·6–4·2)‡	2·3 (1·6–4·4)

Values are median with lower and upper quartiles. PLA_2, phospholipase A_2. $^*P<0·01$ (cerulein with *versus* without inhibitor); $^†P<0·05$, $^‡P<0·01$, $^§P<0·002$ (taurocholate with *versus* without inhibitor) (Wilcoxon test)

$P<0\cdot002$). In taurocholate-induced acute pancreatitis, type I PLA$_2$ protein concentration and type I PLA$_2$ activity in the pancreas of the animals treated with the PLA$_2$ inhibitor were significantly raised ($P<0\cdot01$) compared with values in untreated animals, and values were similar to those seen in the normal pancreas (*Fig. 3b*).

Histomorphology

Over time, there was increased tissue destruction and inflammation in untreated animals with taurocholate-induced acute pancreatitis, whereas changes were moderate in rats treated with the PLA$_2$ inhibitor, especially in the peripheral segments III and IV. In segments I and II, the sites of disease induction, animals in the treated and untreated groups showed similar histological changes during the observation period, as expected (upper range in *Fig. 4*). In segment IV, tissue destruction was reduced by the inhibitor (lower range in *Fig. 4*). Significant differences between the two groups were found ($P<0\cdot01$) for the median sum in the Spormann histological scores (including oedema, pancreatic parenchymal necrosis, fat necrosis, inflammation and haemorrhage) in segment III at 3 and 12 h.

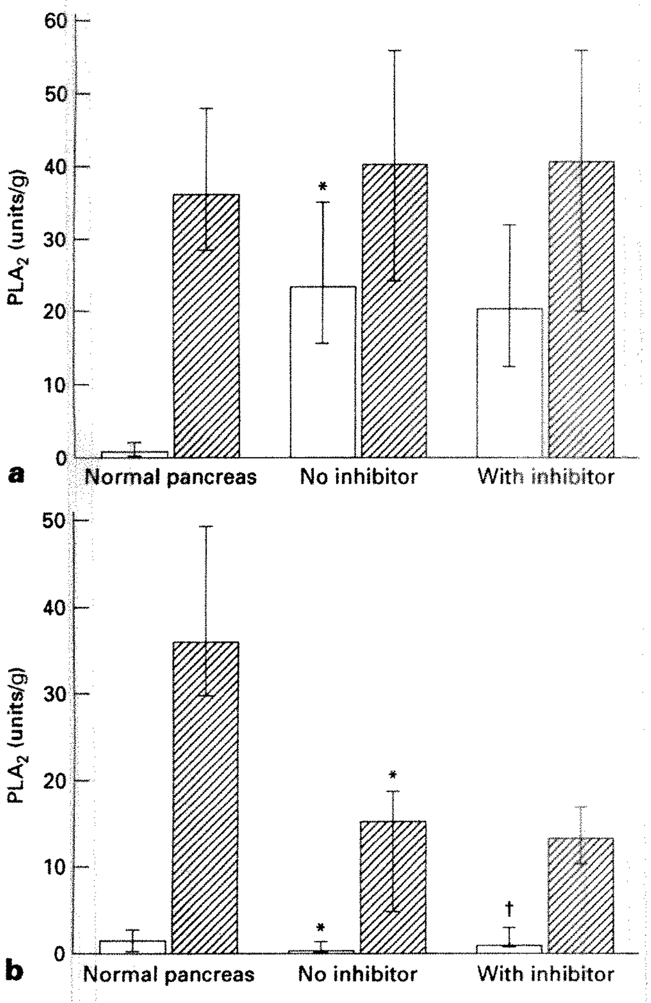

Fig. 3 Type I (□) and type II (▨) phospholipase A$_2$ (PLA$_2$) activity in normal pancreas and pancreas with or without the PLA$_2$ inhibitor in a cerulein-induced acute pancreatitis and b sodium taurocholate-induced acute pancreatitis. Values are median with lower and upper quartiles. $^*P<0\cdot002$ *versus* normal pancreas; $^\dagger P<0\cdot01$ *versus* type I PLA$_2$ with no inhibitor (Wilcoxon test)

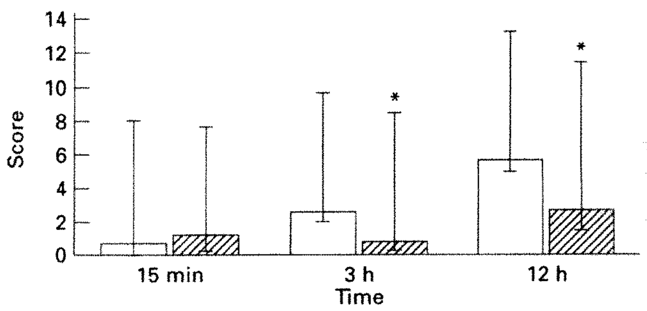

Fig. 4 Quantitative histological analysis of the pancreas from haematoxylin and eosin-stained specimens in taurocholate-induced acute pancreatitis. Comparison of the median sum in the Spormann histological scores *versus* time in segment III for animals with (▨) and without (□) the phospholipase A$_2$ inhibitor. The upper range represents the median in segments I–II and the lower range represents the median in segment IV. $^*P<0\cdot01$ *versus* no inhibitor (Wilcoxon test)

Discussion

Acute pancreatitis is classified clinically into mild and severe forms[24]. The majority of patients suffer from mild acute pancreatitis, a self-limiting disease which responds well to conservative treatment. Up to 20 per cent of patients with acute pancreatitis, however, proceed to a clinically severe form involving both pancreatic and extrapancreatic necrosis, with systemic inflammatory response syndrome and organ complications. Although the initial steps in the pathogenesis of acute pancreatitis are not fully understood, the term 'autodigestion', introduced by Chiari in 1896, summarizes the prevailing concept that the acute inflammation is triggered by the activation of digestive enzymes[25,26]. Protease inhibitors (such as aprotinin and gabexate mesilate), hormones (such as calcitonin, glucagon and somatostatin) and atropine have been studied clinically as possible specific treatments for acute pancreatitis, without success[12,13,27].

PLA$_2$ is the key enzyme in arachidonic acid metabolism, and causes the release of eicosanoids[28]. The enzyme is believed to play an important part in acute inflammatory diseases[1–8]. In acute pancreatitis, increased serum PLA$_2$ activity has been found to correlate with the severity of the disease and the pulmonary impairment[6–8]. On the other hand, measures of pancreatic PLA$_2$ protein concentration have shown no relationship, making it probable that there are two different PLA$_2$ isoenzymes. Indeed, two different types of secretory PLA$_2$ are currently recognized: type I PLA$_2$, which is pancreatic in origin, and type II PLA$_2$, stemming from a non-pancreatic source[9].

Type I PLA$_2$ has been reported to have little activity in hydrolysing cell membranes and in inducing severe inflammatory reactions[29–31], and recent published investigations indicate that the non-pancreatic type II PLA$_2$ plays the central role in the development of local and systemic complications in human acute pancreatitis[4,6–8,32]. The present findings showed marked changes in type II PLA$_2$ activity 3 h after administration of 3 per cent sodium taurocholate stimulating severe acute pancreatitis, whereas type I PLA$_2$ activity did not change significantly.

Kawai *et al.*[33] reported similar findings for a 5 per cent solution of sodium taurocholate with a similar method for the measurement of PLA_2 activity[33]. These findings and the present results indicate that the increase in total PLA_2 activity is caused by the increase in type II PLA_2 activity in the severe model of acute pancreatitis.

In the cerulein model, type II PLA_2 activity showed no change either during cerulein infusion or within the first 12 h. In contrast, in this model the type I PLA_2 protein concentration and type I PLA_2 activity in serum and pancreatic tissue increased rapidly after the induction of acute pancreatitis, with peak values after 3 h. However, these increases in type I PLA_2 had no influence on clinical course or histomorphological findings, which further supports the theory that circulatory as well as local pancreatic PLA_2 is harmless in humans and animals[29–31].

In taurocholate-induced acute pancreatitis, the new low molecular weight PLA_2 inhibitor caused a significant decrease in total PLA_2 activity, mainly by decreasing type II PLA_2 activity. In untreated rats in the cerulein model of acute pancreatitis, where only type I PLA_2 activity increased while type II PLA_2 activity remained constant, there was a decrease in total PLA_2 activity owing to the inhibition of type II PLA_2 activity. Therefore, the PLA_2 inhibitor seems to act mainly on the type II PLA_2 isoform, although *in vitro* studies have shown an additional inhibitory capacity against pancreatic PLA_2 activity.

The decreased levels of type I PLA_2 protein concentration in the tissues and the activities of type I and type II PLA_2 24 h after the induction of acute pancreatitis with sodium taurocholate are explainable by denaturation and inactivation of the enzyme proteins in the necrotic and acid milieu. Support for this theory comes from studies of the enzymes in pancreatic necrosis in human acute pancreatitis. The lowest PLA_2 activity was found in specimens with total pancreatic necrosis[34]. In contrast, tissue type I PLA_2 protein concentration and type I PLA_2 activity in this severe model of acute pancreatitis were unchanged in animals treated with the PLA_2 inhibitor, and were comparable to those found in normal pancreas. This points to the fact that the inhibitor, as a result of its inhibition of type II PLA_2 activity, has the potential for protecting acinar cells from destruction, which may explain the unchanged type I PLA_2 protein concentration and type I PLA_2 activity. This theory is also supported by histomorphological analysis, in which tissue damage and inflammatory reactions remained significant under the influence of the PLA_2 inhibitor.

Findings in the present study lead to the following conclusions. Non-pancreatic type II PLA_2 in both human and experimental severe acute pancreatitis plays an important pathophysiological role. The new low molecular weight PLA_2 inhibitor decreases total catalytic PLA_2 activity. This decrease is caused by the inhibition of non-pancreatic type II PLA_2 activity. The PLA_2 inhibitor reduces tissue destruction and protects pancreatic acinar cells. These findings are important because there is currently no specific treatment available for acute pancreatitis in humans[12,13,27]. This PLA_2 inhibitor holds promise as a treatment for acute pancreatitis and warrants further investigation.

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Laparoscopic cholangiography: a prospective study

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Background The place of cholangiography has been controversial in the conventional and now in the laparoscopic setting. The aim of this study was to evaluate laparoscopic cholangiography and compare use of a portable C-arm image intensifier with conventional radiography.

Methods One hundred and ninety-seven consecutive patients undergoing laparoscopic cholecystectomy were randomized before operation to cholangiography by either C-arm image intensifier or conventional radiography. Data were collected on a pro forma completed immediately after the operation.

Results Cholangiography was successful in 93·0 per cent of patients. Cholangiography with an image intensifier was significantly faster. In 19 patients the ductal system was obscured by a cannula; in 17 of these cases a metal cannula was used. In 31·6 per cent of patients the clip on the cystic duct was within 1 cm or less of the common bile duct (CBD).

Conclusion Laparoscopic cholangiography is a safe procedure. Use of an image intensifier should be the preferred method of obtaining images. Metal cannulas are more likely to obscure the ductal system. The proximity of the clip on the cystic duct to the CBD highlights the potential for injury caused by electrocautery or erroneous clip application.

Ever since Mirizzi described the first operative cholangiogram in 1937[1] the subject has evoked considerable interest. In recent years the debate has centred around whether laparoscopic cholangiography should be performed selectively or routinely. Grace *et al.*[2] felt that peroperative cholangiography may be indicated in selected patients at risk of common bile duct (CBD) stones or in those in whom the biliary anatomy is unclear. Others, however, subscribe to the view that it sets operative priorities and improves surgical skill and technique[3].

In a recent survey of surgeons carrying out laparoscopic cholecystectomy, however, only 15 per cent undertook routine cholangiography, 33 per cent performed cholangiography selectively and 52 per cent never performed the procedure[4].

As well as the detection of unsuspected ductal stones[5], proponents of laparoscopic cholangiography also cite identification of variations in biliary anatomy[6,7], the reduction in risk of CBD injury[8] as well as the detection of unsuspected operative damage at an early stage in support of laparoscopic cholangiography. A recent study by Kullman *et al.*[9] suggested that early detection of injury led to prompt repair and thereby a reduction in the morbidity associated with a delayed diagnosis.

The aim of this study was to evaluate laparoscopic cholangiography by comparing use of a portable C-arm image intensifier with conventional radiography.

Patients and methods

Some 197 consecutive patients undergoing laparoscopic cholecystectomy by two surgeons (C.D.A., I.M.M.) between September 1992 and January 1995 were included in the study. There were 38 men (mean age 59 (range 24–80) years) and 159 women (mean age 52 (range 17–83) years).

A selective policy of endoscopic retrograde cholangiopancreatography (ERCP) was practised in patients with the standard risk factors for CBD stones[10]. The patients were randomized before operation by opening envelopes to determine the method of cholangiography. Cholangiography was performed, either with a C-arm image intensifier (Stenoscop 9000, IGE Medical Systems, Loncin, Belgium) or by conventional radiography.

Following insertion of a 14-Fr Quickcath (Baxters, Norfolk, UK) percutaneously, a standardized technique of cholangiography was used for all patients[11]. A 4-Fr umbilical catheter (Portex, Hythe, UK) was manipulated into the cystic duct and held in place by a loosely applied ligaclip. Contrast medium (Sodium diatrizoate; Schering, Berlin, Germany) was injected and two films taken as routine for either mode of cholangiography. Traction on the gallbladder was not applied at the time of cholangiography.

Image magnification was minimized by using the maximum focus–film distance and the minimum subject–film distance, and by obtaining all image intensifier hard copies on the largest available field size. The hard copy films were subsequently reviewed independently by a radiologist (D.H.).

Data were collected on a pro forma which was completed by the surgeon immediately after each operation. The mode of cholangiography, the success of the procedure and reasons for failure were noted. The time required for the procedure (insertion of Quickcath to visualization of the biliary system), as well as the completeness of cholangiogram (visualization of intrahepatic/extrahepatic ducts and duodenum), were recorded. The distance between the cystic duct clip and CBD was documented, as were the detection of CBD stones and anatomical anomalies.

Results

In 11 of the 197 patients, cholangiography was not attempted but in eight of these patients conversion took place before Calot's triangle was exposed. In a further 13 patients, cholangiography was attempted but unsuccessful for reasons outlined in *Table 1*, resulting in a success rate of 93·0 per cent. Of the 173 patients for whom successful cholangiograms were obtained, 83 had been randomized

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Table 1 Patients in whom laparoscopic cholangiography was either not attempted or was attempted but unsuccessful

	No. of patients
Cholangiography not attempted	
Unclear anatomy	4
Cystic duct transected	3
Adhesions	2
Bleeding	2
Total	11
Cholangiography attempted but unsuccessful	
Cystic duct too small	10
Contrast leak	2
Radiography equipment failure	1
Total	13

Table 2 Duration of laparoscopic cholangiography and operation using either image intensifier or standard radiography

	Image intensifier	Standard radiography
Cholangiography (min)	15 (7–30)	23 (10–50)*
Operation (min)	71 (29–140)	80 (35–140)

Values are mean (range). $^*P<0.0001$ *versus* image intensifier (unpaired t test)

previously to image intensifier and 90 to conventional radiography.

The mean times required for cholangiography and the duration of the operation are shown in *Table 2*. The difference in times for cholangiography were statistically significant ($P<0.0001$, unpaired t test).

The surgeon assessed the images to be complete in 90 per cent of cases in which the image intensifier was used and 86 per cent with conventional radiography, whereas the radiologist's assessment was 81 and 82 per cent respectively. The radiologist, however, did not have the benefit of real-time imaging in assessing the images obtained with the intensifier.

The cannula obscured part of the duct system in 19 patients, but in only two of these was a disposable cannula used. (The type of cannula used was determined by the routine practice of the two surgeons.) In 14 patients (15·6 per cent) more than the standard two images were required and in the majority of cases this was because of incorrect positioning of the patient or resiting of the cannula in the conventional radiography group.

The distance between the ligaclip on the cystic duct to the CBD was measured from the radiographic films of both groups. The 'critical length' was recorded in 165 cases, in eight of the 173 successful laparoscopic cholangiographies the operator omitted to record the distance. In almost one-third of cases (31·6 per cent) the 'critical length' was 1 cm or less. There was no correlation between 'critical length' and conversion rate (*Fig. 1*).

Fourteen patients were found to have CBD calculi at the time of operation. Three of these had had a mildly raised alkaline phosphatase level at the time of initial presentation but the level had returned to normal before operation. One patient had had jaundice before admission and had undergone ERCP and sphincterotomy. The remaining ten had no clinical or biochemical features to suggest CBD stones. Of the 14 cases, five were converted to an open procedure after calculi were revealed and six were successfully dealt with by postoperative ERCP. In three of the patients the operation had already been converted to an open procedure for other reasons when calculi were discovered. The overall conversion rate was 10·2 per cent (*Table 3*). There were no negative bile duct explorations in the study and none of the patients have returned with calculi during follow-up.

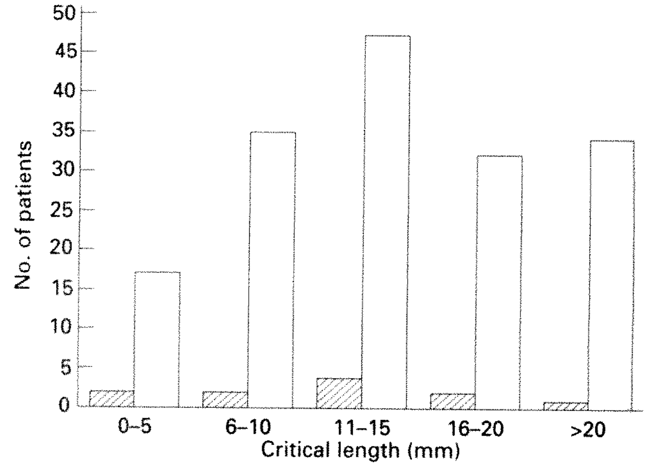

Fig. 1 'Critical length' (clip on cystic duct to common bile duct) in relation to total number of procedures (☐) and conversions to open cholecystectomy (▨)

Table 3 Reasons for conversion from laparoscopic to open cholecystectomy

	No. of operations
Unclear anatomy	7
CBD stones	5
Bleeding	3
Adhesions	2
Cystic duct transected	2
CBD injury	1
Total	20 (10·2)

Values in parentheses are percentages. CBD, common bile duct

Although subjective, in terms of technical difficulty, the laparoscopic cholangiography procedure was considered 'easy' in 59 per cent of cases by the operator, 'moderately difficult' in 29 per cent and 'difficult' in 12 per cent.

Discussion

The success rate for cholangiography of 93·0 per cent is in keeping with other studies[6,12,13], although it has been postulated that success rates will increase with greater experience in the procedure[10]. It is acknowledged that variations in technique exist[14] although it has not been determined as yet which one should be adopted universally.

Laparoscopic cholangiography may have a place in the detection of unsuspected CBD stones. Despite a selective ERCP policy the present incidence of CBD calculi at operation was 7 per cent but this is in agreement with other series[15,16]. The relevance of discovering clinically unsuspected stones during routine laparoscopic cholangiography has been questioned in the presence of an effective ERCP service[17], but the optimum management of these stones will no doubt continue to evolve for the foreseeable future with the refinement and likely establishment of laparoscopic exploration of the CBD.

It has been suggested that fluoroscopy should reduce the time required for cholangiography compared with standard radiography[17] and this has been substantiated in the present study. Although there does not seem to be a difference in the completeness of cholangiogram obtained by either method, fluoroscopy offered more versatility by real-time imaging. For example, the table can be tilted and drugs such as glucagon or morphine administered to improve filling and drainage of the complete biliary tree.

Misinterpretation of a cholangiogram may occur when an incomplete examination of the entire biliary tree has been accepted[18]. Over 80 per cent of these cholangiograms were considered complete. A scoring system[19] to assess quality of cholangiogram was not employed in this study, but both surgeon and radiologist used the same criteria to determine completeness and there were no significant differences in their findings. However, metal cannulas were far more likely to obscure the image than disposable cannulas, especially in conventional radiographic imaging.

The major concern during laparoscopic cholecystectomy is iatrogenic bile duct injury, and careful dissection and clear visualization of the anatomy are of paramount importance; despite this the actual junction of the cystic duct and CBD may not be seen easily. A problem in this critical area has been alluded to[13] where a short cystic duct and subsequent superolateral retraction of the gallbladder causes 'tenting' of the CBD, which can be mistaken for the cystic duct and clipped. The present study draws attention to the distance between the clip on the cystic duct and the CBD as this may be important in laparoscopic dissection. The use of electrocautery, for example, before clip application highlights the importance of being confident in the local anatomy if thermal injury to the CBD is to be avoided, bearing in mind that injury can be caused either directly during dissection (immediate perforation) or by secondary extension of thermal damage (delayed perforation)[20]. Open cholecystectomy series report an injury rate to the CBD of 0·2 per cent, whereas the best figures for laparoscopic work remain above 0·3 per cent[21]. While some claim that cholangiography will reduce the rate of CBD injury[22] others suggest that it is more likely to lead to early detection of such injury[23], and there are those who feel that routine use of cholangiography does not prevent it[2]. One CBD injury occurred in this study and cholangiography led to immediate recognition of the injury.

The conversion rate of 10·2 per cent was perhaps a little higher than reported previously[24,25], but there does seem to have been a reduction as the study progressed. Mitchell *et al.*[26] stated that cholangiography is more difficult in the laparoscopic setting, but the present study suggests that the laparoscopic surgeon can carry out this procedure without too much difficulty.

Laparoscopic cholangiography is a safe procedure and, even if not used routinely, every surgeon practising laparoscopic cholecystectomy should have the ability to perform the technique. This study shows that cholangiography with an image intensifier is preferable to standard radiography and metal cannulas should be avoided.

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Multidisciplinary approach to biliary complications of laparoscopic cholecystectomy

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Background Bile leaks and bile duct strictures are major complications of cholecystectomy which increased in incidence after the introduction of laparoscopic surgery. The management and outcome of these complications following the introduction of laparoscopic cholecystectomy was reviewed.

Methods Eighteen patients of median age 45 (range 22–70) years were treated between January 1992 and December 1995. Six patients had a common hepatic duct (CHD) stricture, four following a failed previous repair. Nine patients had bile leaks from bile duct transection (four), cystic stump (four) or segment V duct (one). Two patients had partial bile duct damage with primary sutured repair at time of cholecystectomy. One patient had recurrent haemobilia from a hepatic artery pseudoaneurysm.

Results Cystic stump or segment V leaks were treated successfully by endoscopic stenting (median follow-up 42 months). Roux loop biliary reconstruction was carried out in nine patients: two CHD strictures, three of the four failed primary CHD repairs and four bile duct transections. All had normal liver function test results at median follow-up of 30 months. The two patients with partial duct injuries repaired at initial surgery required no further intervention. The right hepatic artery aneurysm was successfully embolized. There have been no deaths or major complications of endoscopic, radiological or surgical intervention.

Conclusion Endoscopic stenting successfully treats cystic stump and segment V duct leaks. Duct strictures, including failed initial repairs and transections, have a good outcome with Roux-en-Y loop reconstruction.

Laparoscopic cholecystectomy has become the preferred treatment of symptomatic gallstones since its introduction in the UK in 1990. However, prospective audits reported a fourfold to eightfold increase in biliary complications compared with those seen in the 'open' era[1,2]. Whether this is related to the technique *per se* or is merely associated with a surgical 'learning curve' has not been established. The mechanism and nature of biliary complications following laparoscopic surgery are different from those at open surgery[3]. Their management and outcome therefore require the same critical evaluation as the introduction of the procedure itself[1,2]. An analysis was made of the management and outcome of patients with biliary complications over a 4-year period following the widespread introduction of laparoscopic cholecystectomy.

Patients and methods

Data were reviewed on all patients with a biliary complication of laparoscopic cholecystectomy treated in this institution between January 1992 and December 1995. Complete data capture was ensured by referring to the computer database for endoscopic retrograde cholangiopancreatography (ERCP) and to the radiology database for percutaneous transhepatic cholangiography (PTC).

Eighteen patients were treated over this 4-year period. Patient characteristics, cholecystectomy details, nature of the biliary complication and previous biliary surgery are shown in *Table 1*. Eight laparoscopic cholecystectomies had been performed by consultants and ten by higher surgical trainees. All were done electively but three had evidence of acute cholecystitis at operation, confirmed by subsequent histological examination. Intraoperative cholangiography (IOC) had been performed in four patients. Of these, two developed a cystic duct stump leak (patients 3 and 4), one had a partial transection of the common hepatic duct (CHD) which was noted on IOC and repaired by primary suture (patient 14), and the fourth patient had normal IOC findings but subsequent complete transection of the CHD (patient 10). One patient had undergone preoperative ERCP and stone removal.

In six patients the biliary complication was noted at laparoscopic cholecystectomy (patients 13–18). These patients had conversion to an open operation and primary repair was performed (*Table 1*). In-patient stay in this group ranged from 7 days to 2 months (median 2 weeks). Four of these patients required further management following a failed primary repair with onset of jaundice or cholangitis due to anastomotic stricturing.

In 12 patients laparoscopic cholecystectomy had been completed. In three patients some difficulty had been encountered as a result of adhesions (one) or bleeding (two). Nine of the 12 patients in this group had been discharged from hospital (on postoperative days 2–12) and three were transferred directly for further management. Five of the 12 patients had undergone exploratory laparotomy for a suspected bile leak before referral (patients 2, 4, 6, 11 and 12). None had undergone full cholangiography before laparotomy. A bile leak was

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Table 1 Patient details, timing and nature of biliary complication, and operation before referral

Patient no.	Age (years)	Sex	Time to symptoms after laparoscopic cholecystectomy	Biliary complication (Bismuth type[4])	Operation before referral
1	65	F	4 days	Cystic stump leak	None
2	29	F	2 days	Cystic stump leak	None
3	68	F	5 days	Cystic stump leak	None
4	22	F	4 days	Cystic stump leak	Laparotomy and oversewing of leaking stump
5	45	M	4 days	Segment V duct leak	Laparotomy and drainage
6	49	F	6 weeks	RHA pseudoaneurysm	Laparotomy and adhesiolysis
7	41	F	3 weeks	CHD stricture (II)	None
8	30	F	10 days	CHD and RHD stricture (III)	None
9	53	F	8 days	CHD transection (IV)	None
10	28	F	10 days	CHD transection (IV)	None
11	66	F	2 days	CHD transection (IV)	Laparotomy and bile drainage
12	47	F	4 days	CHD transection (IV)	Laparotomy and bile drainage
13	47	M	Operative repair	Partial bile duct transection (II)	Open duct repair over T tube
14	38	F	Operative repair	Partial bile duct transection (II)	Open duct sutured repair
15	70	F	5 months	CHD transection (IV)	Open duct-to-duct repair over T tube
16	32	F	8 months	CHD transection (III)	Open duct-to-duct repair over T tube
17	45	F	4 months	CHD transection (III)	Open Roux loop reconstruction over T tube
18	40	F	17 months	CHD transection (II)	Open Roux loop repair

RHA, right hepatic artery; RHD, right hepatic duct; CHD, common hepatic duct

Table 2 Indication for referral and management in hepatopancreaticobiliary unit

Patient no.	Presentation	Biliary complication on presentation to unit	Treatment	Follow-up* (months)
1	RUQ peritonitis	Cystic stump leak	Ultrasonographically guided drainage; nasobiliary drain; endoscopic stent insertion for 6 weeks	24
2	RUQ peritonitis	Cystic stump leak	Nasobiliary drain; endoscopic stent insertion for 6 weeks	18
3	RUQ peritonitis	Cystic stump leak	Ultrasonographically guided drainage; nasobiliary drain; endoscopic stent insertion for 8 weeks	42
4	RUQ peritonitis	Cystic stump leak	No further treatment	48
5	RUQ peritonitis	Segment V bile leak	Ultrasonographically guided drainage; nasobiliary drain; endoscopic stent insertion for 8 weeks	48
6	Jaundice and melaena	RHA pseudoaneurysm	Coil embolization of pseudoaneurysm	18
7	Jaundice and itching	CHD stricture	Roux-en-Y hepaticojejunostomy	48
8	Pain and jaundice	CHD and RHD stricture	Endoscopic balloon dilatation; Roux-en-Y hepaticojejunostomy	60
9	Jaundice and peritonitis	CHD transection	Roux-en-Y hepaticojejunostomy	16
10	Bile ascites	CHD transection	Roux-en-Y hepaticojejunostomy	48
11	Generalized peritonitis	CHD transection	Ultrasonographically guided drainage; Roux-en-Y hepaticojejunostomy	26
12	Generalized peritonitis	CHD transection	Roux-en-Y hepaticojejunostomy	18
13	No further symptoms	Partial division of CHD	No further treatment	26
14	No further symptoms	Partial division of CHD	No further treatment	24
15	Cholangitis	Stricture of initial repair	Roux-en-Y hepaticojejunostomy	36
16	Jaundice and itching	Stricture of initial repair	Roux-en-Y hepaticojejunostomy	30
17	Pain	Stricture of initial repair	Roux-en-Y hepaticojejunostomy; stricture of RHD–jejunal anastomosis, treated by percutaneous dilatation	24
18	Cholangitis	Stricture of initial repair	Percutaneous balloon dilatation at 17 and 58 months	60

*Three-monthly symptom review and liver function tests. RUQ, right upper quadrant; CHD, common hepatic duct; RHD, right hepatic duct; RHA, right hepatic artery confirmed in four of the five patients, but in only one was the site of leak identified and secured. Patients in this group were referred between 3 days and 11 months after laparoscopic cholecystectomy and 1–21 (median 3) days after a biliary complication was suspected. Laparotomy findings are also shown in *Table 1*.

Results

The indication for referral, clinical and radiological findings, treatment and outcome of the patient group are given in *Table 2*.

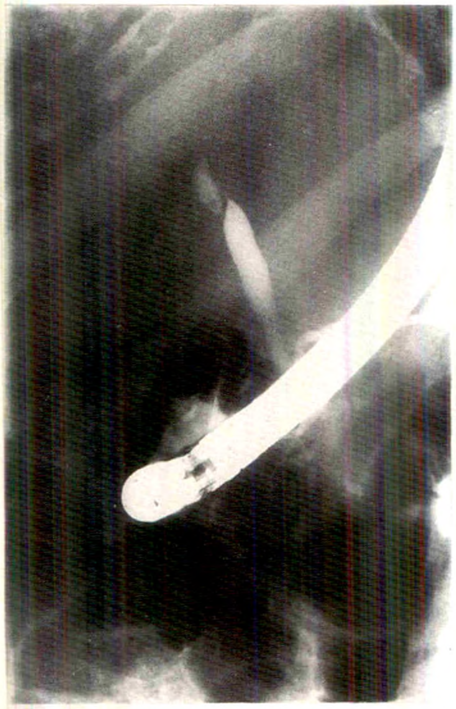

Fig. 1 Endoscopic retrograde cholangiopancreatography demonstrating complete occlusion of the common hepatic duct. There is no visualization of the intrahepatic bile ducts and therefore percutaneous cholangiography is essential to establish the extent of biliary injury

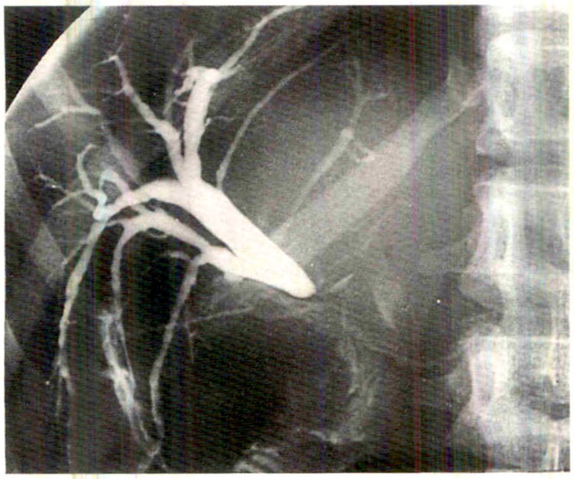

Fig. 2 Percutaneous transhepatic cholangiography demonstrating a stricture at the site of a biliary–enteric anastomosis. The stricture developed following a bile leak at the initial anastomosis

Abdominal ultrasonography was performed following admission in 15 patients. Of the nine patients with bile leaks (patients 1–5 and 9–12), subhepatic collections were found in four (drained percutaneously) and generalized free fluid in three. Dilated intrahepatic ducts were found in all six patients with bile duct strictures (patients 7, 8 and 15–18).

ERCP was performed in 13 patients and established the nature of the biliary complication in six. Patients in whom ERCP showed complete biliary obstruction (*Fig. 1*) proceeded to PTC to demonstrate the intrahepatic bile ducts (*Fig. 2*). PTC successfully demonstrated the entire intrahepatic biliary tree in eight patients with no associated complications. Selective angiography was performed in eight patients and showed right hepatic artery pseudoaneurysm in one (patient 6) and occlusion in three (*Fig. 3*).

Of the five patients with cystic stump or segment V bile leaks, one was successfully identified and secured at laparotomy before referral. The other four underwent percutaneous drainage of collections along with

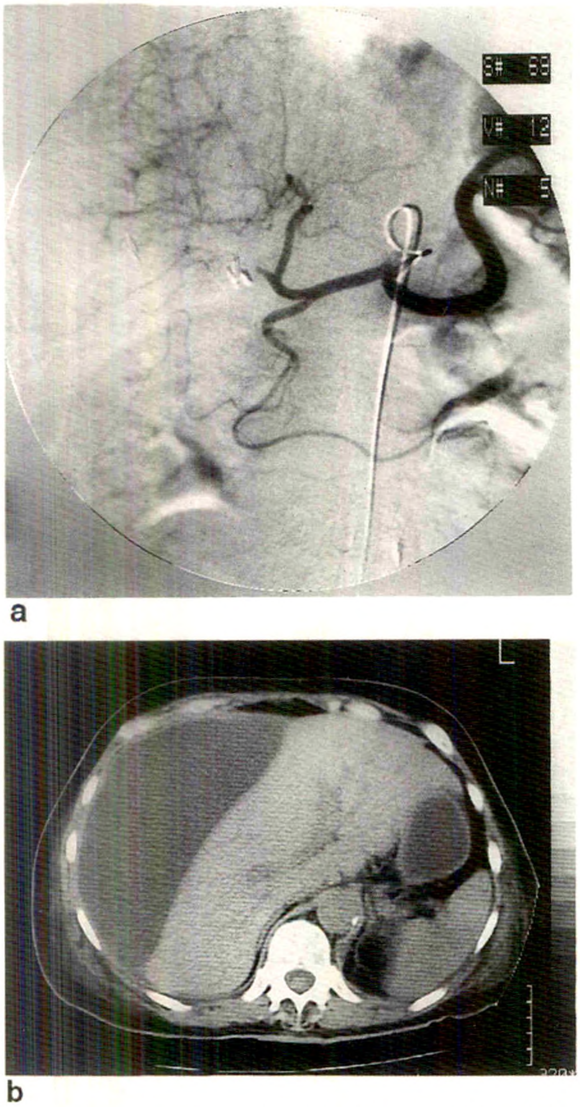

Fig. 3 **a** Selective hepatic angiography demonstrating a right hepatic artery occlusion from a clip. **b** The associated computed tomogram demonstrating right lobe atrophy and a subphrenic bile collection

endoscopic insertion of a nasobiliary drain (three patients), followed by stenting (four) for a period of 6–8 weeks. There were no immediate or subsequent treatment-related complications (median follow-up 42 (range 18–48) months).

Biliary reconstruction was performed in nine patients. Two had bile duct strictures (patients 7 and 8), four had complete bile duct transection (patients 9–12) and three had a failed previous biliary reconstruction and anastomotic stricturing (patients 15–17). Reconstruction was by Roux-en-Y hepaticojejunostomy in all cases with formation of a percutaneous access loop in patients with Bismuth type IV[4] injuries (five patients). Eight of the nine patients are asymptomatic and have had no further biliary complications (median follow-up 30 (range 16–60) months). All have normal liver function. One patient (no. 17), who was referred following failed initial Roux loop repair, has had persistent pain which improved following percutaneous balloon dilatation of a radiological stricture at the right hepaticojejunal anastomosis.

Biliary balloon dilatation was used in three patients with strictures. One failed after 2 months (patient 8) with subsequent Roux loop reconstruction. Two were successful (patients 17 and 18) with a follow-up of 12 and 58 months.

In the patient with recurrent haemobilia (patient 6), selective angiography revealed a right hepatic artery pseudoaneurysm which was successfuly treated by transarterial coil embolization (follow-up 18 months). Two patients (nos 13 and 14) referred for evaluation following an operative partial injury to the bile duct required no further treatment.

Discussion

Prospective audits in England and Wales[2], the west of Scotland[1,5] and the Netherlands[6] have reported biliary injury rates following laparoscopic cholecystectomy of 0·3–0·8 per cent, similar to those found in large series from Europe (0·33 per cent)[7] and the USA (0·25 per cent[8] and 0·5 per cent[9]) but higher than the one in 1000 bile duct injury rate reported by selected centres with open cholecystectomy[10–13]. Referral centres have also reported an increase in bile duct injuries following the introduction of laparoscopic cholecystectomy[6,14,15]. However, some single-centre comparisons have shown no increase in complications and reduced morbidity and mortality rates associated with the laparoscopic procedure[16,17], and more recent regional cholecystectomy audits have shown an incidence of bile duct injuries similar to that of open surgery[5,18]. The present study provides no insight into the true incidence of bile duct injuries in the UK, as most patients were referred only after a failed initial attempt at bile duct repair or failure to control a bile leak.

The immediate management of patients found to have a bile duct injury at the time of laparoscopic cholecystectomy is controversial. Primary suture for a localized injury to the bile duct was satisfactory in this and other studies[18,19], although the late development of strictures is well recognized[20]. With complete duct transections, primary duct to duct repair is associated with a high failure rate, as seen in two patients in the present series and in 13 in the series of Stewart and Way[19,21,22]. A primary Roux-en-Y repair has been reported as satisfactory from the audit by Russell and colleagues[18]. However, a failed Roux loop repair leading to a bile leak and subsequent stricture, as found in one of the present patients, considerably increases the difficulty of obtaining a satisfactory outcome from revisional biliary surgery[19]. If expertise in forming a Roux-en-Y loop to a non-dilated bile duct is not available, biliary drainage and transfer to a hepatobiliary centre may be advisable.

There has been much debate on the value of IOC. Supporters stress that surgically relevant biliary tract anomalies are common[23]. Only one patient in the present series had a major biliary tract anomaly and the injury was unrelated to this[24]. In one patient IOC demonstrated a bile duct injury allowing primary duct repair over a T tube. Routine IOC increases the time required for cholecystectomy and is associated with a small risk of biliary complications[25]. However, it would ensure the earlier detection of some bile duct injuries and hence improve the overall results of surgical treatment[23]. The technique used for laparoscopic cholecystectomy may be a more important factor in the prevention of bile duct injuries[26].

In this study the majority of biliary complications were detected in the early postoperative period, although in three-quarters this was after discharge from hospital. An occult presentation can occur even with major bile duct injuries[24,27] and a delay in diagnosis and satisfactory treatment is a considerable disadvantage to the long-term outcome of bile duct injuries[4,28]. In this series, referral occurred promptly at a median of 3 days (range from 1 day to 3 weeks) after a biliary tract complication was suspected.

The importance of cholangiographic assessment before surgery for a biliary tract complication has been emphasized previously by Stewart and Way, duct repair failing if no or incomplete cholangiography was obtained before operation[19]. Of the four patients in this series who underwent further surgery for bile leakage before referral, this was successful in one; the other patients achieved only drainage of bile collections. None had undergone cholangiography.

The authors have found oral and intravenous contrast-enhanced computed tomography to be useful in detecting previously undrained collections and lobar liver atrophy associated with vascular occlusion[29]. Selective hepatic angiography was performed in eight patients, of whom four had significant findings including a right hepatic artery occlusion in three and an aneurysym of the right hepatic artery in one. Vascular occlusion was associated with more severe injuries to the biliary tract, three of the four patients having Bismuth type IV duct damage[30], for which reconstruction is reported to be less successful[19,31]. Experience of this problem in liver transplantation may be an advantage in the management of these bile duct injuries[32–36]. Haemobilia is an unusual complication of laparoscopic cholecystectomy[37], although pseudoaneurysm of the right hepatic artery has been reported[38–43] and most have been treated successfully by embolization.

The definitive treatment of bile duct injuries remains controversial. In this and previous studies bile leak from the cystic duct stump has been managed successfully by endoscopic stenting, endoscopic sphincterotomy alone being unsatisfactory[31]. With common bile duct injuries some groups support the use of endoscopic biliary stents[31], others suggesting that this merely delays satisfactory surgical treatment[19]. In the present series a Roux-en-Y jejunal loop without stenting was used for strictures or transection of the bile duct[19,22,44,45]. Although long-term follow-up data are required, excellent initial results have been obtained with surgical reconstruction for major bile duct injuries (median follow-up 30 months) and endoscopic stenting for cystic stump or segment V duct leaks (median follow-up 42 months). There have been no deaths or major complications.

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Mortality following elective infrarenal aortic reconstruction: a Joint Vascular Research Group study

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Background This study aimed to define the cause of death in patients undergoing elective infrarenal aortic reconstruction.

Methods Members of the Joint Vascular Research Group who had collected details prospectively of patients undergoing elective aortic reconstruction provided information on those who died.

Results Details of 3786 patients were obtained. Some 171 patients died (133 following abdominal aortic aneurysm (AAA) and 38 after aortofemoral bifurcation graft (AFBG) for occlusive disease). The mortality rate following AAA repair was 4·8 per cent, rising to 16 per cent if repair was combined with either renal or distal reconstruction ($P < 0·001$). Similar results were obtained with AFBG (3·4 and 11 per cent respectively, $P < 0·001$). The first major complication encountered was cardiac (39·8 per cent), followed by bleeding (20·5 per cent), respiratory (13·5), and gut (5·3 per cent), or limb ischaemia (6·4 per cent). Bleeding was commoner following reconstruction for aneurysm compared with that for occlusive disease ($P < 0·05$). Eighty-six patients (50·3 per cent) died from the first major complication. Of the remainder, 45 (53 per cent) developed multisystem organ failure (MSOF). The most commonly involved systems were cardiac, respiratory and renal.

Conclusion Cardiac problems were the major cause of death following infrarenal aortic reconstruction. MSOF is the 'final common pathway' in about half of the patients who survive the initial complication.

Patients with an abdominal aortic aneurysm (AAA) have a high prevalence of both symptomatic and asymptomatic cardiac disease[1]. Cardiac problems are frequent following aortic reconstruction. Major cardiac problems (cardiac death, myocardial infarction or left ventricular failure) have been reported in 15 per cent of patients undergoing aortic reconstruction[2]. Less serious cardiac events occur in 25 per cent. The incidence of silent postoperative ischaemic changes may be even higher[3]. A recent report[4] has challenged the view that cardiac events are the commonest cause of death following aortic reconstruction, suggesting that multisystem organ failure (MSOF) is the leading cause. If this is true, efforts to identify patients with cardiac disease before operation may be misplaced. Alternatively, perhaps cardiac risk factors are being successfully identified and modified before aortic reconstruction, although there is little evidence to support this hypothesis.

The aim of this paper was to define the incidence and cause of death in patients undergoing elective infrarenal aortic reconstruction.

Patients and methods

Data were collected from members of the Joint Vascular Research Group who had collected information prospectively on elective aortic reconstructions. In addition to demographic data, the nature and timing of the first significant adverse event during or after operation were noted. Subsequent progress of the patient was defined. Together with the number and details of patients who died, each surgeon provided the number of elective aortic reconstructions performed during the study interval.

The Detsky index was calculated as described previously[2]. Essentially this is a scoring system whereby points are ascribed to pre-existing risk factors. Coronary artery disease, left ventricular failure, valvular disease, arrhythmias, poor general condition and age over 70 years are all defined and scored. The greater the score, the more likely are postoperative cardiac events[5–7].

MSOF was diagnosed in the presence of failure of more than one of respiratory, renal, cardiovascular, coagulation, central nervous, gastrointestinal or immunological systems[8].

Results

Data were obtained from 20 surgeons, 14 of whom worked in a teaching hospital. Details on 3786 patients having elective aortic reconstruction were obtained. Of these, 171 died. Some 140 deaths (81·9 per cent) occurred during 1990–1995. The majority of patients were men; the median age of the group was 74 (range 48–87) years (*Table 1*). Twenty-five (18·8 per cent) of the 133 patients who had AAA repair and died were over 80 years of age. By contrast, 12 of the 38 patients who died following an aortofemoral bifurcation graft (AFBG) were younger than 65 years. In patients with aortic occlusive disease, the indication for operation was rest pain or ulceration in 25 and incapacitating claudication in the remainder. Aortic reconstruction was combined with other reconstructions in

Table 1 Details of 171 patients who died after elective aortic surgery

	Aortic aneurysm repair	Aortofemoral bypass graft	Total
Men	108	26	134
Women	25	12	37
Median (range) age (years)	76 (60–87)	69 (48–84)	74 (48–87)

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24 patients who died (lower limb revascularization, 14; renal or visceral revascularization, ten).

The mortality rate following AAA repair, whether straight or bifurcated graft, was 4·8 per cent ($n = 2680$). By contrast, when aneurysm repair was combined with either distal or renal reconstruction, the mortality rate rose to 16 per cent of 96 patients ($\chi^2 = 22·3$, 1 d.f., $P < 0·0001$). Similar results were obtained with AFBG for occlusive disease. The mortality rate when AFBG alone was performed was 3·4 per cent in 940 patients. This compared with a mortality rate of 11 per cent in 80 patients who had AFBG combined with a further reconstruction ($\chi^2 = 11·5$, 1 d.f., $P < 0·001$). There was no difference in mortality rates in district general hospitals (DGHs) compared with teaching hospitals. The mortality rate following uncomplicated AAA repair in a DGH was 6·2 per cent of 786 cases, compared with 4·3 per cent of 1849 cases in a teaching hospital ($\chi^2 = 2·8$, 1 d.f., P not significant). Similar results were obtained for AFBG: 2·8 per cent of 177 cases in a DGH compared with 3·5 per cent of 753 cases in a teaching hospital ($\chi^2 = 0·28$, 1 d.f., P not significant).

First major complication encountered (Table 2)

A cardiac event was noted in 68 patients (39·8 per cent), most frequently myocardial infarction. Calculation of the Detsky index in patients sustaining a major cardiac event revealed a median score of 10 (range 0–40). Forty-five patients had a Detsky index of 10 or more. Pre-existing cardiac risk factors in this group of patients included angina (26 patients), myocardial infarction (22) and cardiac arrhythmia (three).

Intra-abdominal bleeding occurred in 32 of 133 patients who died following AAA repair compared with three of 38 after AFBG ($\chi^2 = 4·7$, 1 d.f., $P < 0·05$). Nine of these 35 patients died on the operating table.

Respiratory complications developed in 23 patients. Three patients had a pulmonary embolus and four an overwhelming chest infection. It was impossible to wean the remaining 16 patients off the ventilator. Two patients were initially successfully extubated but required reventilation for respiratory distress. Six of these 16 patients had severe chronic obstructive airway disease (COAD).

Table 2 First major complication encountered in patients who died after elective aortic surgery

	Aortic aneurysm repair ($n = 133$)	Aortofemoral bypass graft ($n = 38$)
Cardiac		
Myocardial infarction	45	13
Arrhythmia	2	3
Cardiac arrest	3	1
Non-specific	1	0
Bleeding (abdominal)	32	3
Respiratory	20	3
Ischaemic leg	9	2
Ischaemic gut	7	2
Renal	6	1
Graft thrombosis	2	5
Stroke	4	3
Sepsis	1	1
Bleeding from groin	0	1
Unclear	1	0

Table 3 Subsequent complications in patients who died after elective aortic surgery

	No. of patients
Died from original problem	86
Subsequent problems developing	
Cardiac	12
Myocardial infarction	3
Arrhythmia	4
Cardiac failure or arrest	4
Non-specific	1
Renal	10
Respiratory	7
Stroke	2
Ischaemic bowel	2
Gastrointestinal haemorrhage	1
Sepsis	1
Multisystem organ failure	45
Unclear	1

The first major complication occurred within 24 h of operation in 84 patients (49·1 per cent) and within 3 days in 134 (78·7 per cent). In 21 patients the event was intraoperative.

Outcome following initial complication

Eighty-six patients (50·3 per cent) died from the first complication. The remainder went on to develop further complications (*Table 3*). Forty-eight of the 68 patients who originally sustained a cardiac event died from that event. Only 37 of the 103 patients who presented initially with a non-cardiac complication died as a result of it ($\chi^2 = 19·6$, 1 d.f., $P < 0·001$).

Of the 85 patients who survived the first complication, 45 (53 per cent) developed MSOF (*Table 4*). The median number of systems involved was 3 (range 2–4).

Fifty patients required 59 reoperations: 22 had a laparotomy for bleeding, 20 a laparotomy for bowel ischaemia and 17 reoperation for limb ischaemia. Seven patients required a major amputation.

Death occurred within 24 h of operation in 22 patients (12·9 per cent) and within 2 days in 44 (25·7 per cent). The median interval between operation and death was 5 days. Most patients (121) died on the intensive therapy unit, 33 died on the surgical ward, ten in the operating theatre, two on a coronary care unit and five on a high-dependency unit.

Discussion

In the 1960s several reports showed that the mortality rate following elective AAA repair was approximately 10 per cent[9,10]. Over the next two decades, with improvements in

Table 4 Multisystem organ failure as the cause of death: systems involved

	No. of patients
Cardiac	20
Respiratory	24
Renal	26
Sepsis	11
Gastrointestinal	5
Coagulopathy	1
Cerebrovascular	4
Not specified	6

surgical, anaesthetic and intensive care techniques, the rate fell to 5 per cent or less, and in some series was down to zero[11]. Results described here are similar to those in other reports. The mortality rate following elective aortic reconstruction may rise over the next few years as the more technically straightforward cases of both occlusive and aneurysmal disease are dealt with successfully by interventional radiology[12].

Combining aortic reconstruction with either renal or distal revascularization significantly increases mortality. Similarly, Bickerstaff *et al.*[13] found that combining AAA repair with a further procedure, whether vascular or non-vascular, almost doubled the mortality rate following AAA repair alone. Another report[14] described a mortality rate of approximately 10 per cent when aortic reconstruction was combined with renal or superior mesenteric artery revascularization. Huber *et al.*[4] reported a mortality rate of 9 per cent for renal plus aortic reconstruction and 16 per cent for aortic reconstruction and revascularization of the leg.

In the present series there was no difference in mortality rates between operations performed in a teaching or district general hospital. Some studies have suggested a higher mortality rate in a DGH[15]. On the other hand, there are reports of aneurysm repair carried out in DGHs with low mortality rates[16]. The important factors in determining mortality are likely to be the enthusiasm and training of the surgeon involved and the number of cases undertaken. Amundsen *et al.*[17], in a series of 279 elective AAA repairs, found a significantly lower mortality rate reported by surgeons who carried out more than ten repairs per year. Mortality rate did not depend on the type of operation or the size of hospital.

This study confirms that cardiac problems are the commonest cause of death. Patients who initially sustain a cardiac complication are more likely to die from that problem than those who suffer other primary complications. In a large multicentre study, Johnston[18] found that two-thirds of deaths following repair of non-ruptured AAA were due to cardiac complications. The study also showed that patients who had a cardiac problem after operation had a 25 per cent mortality rate compared with 1 per cent in those with no cardiac complications. In addition to the features described by Detsky, a history of transient ischaemic attacks[19] and electrocardiographic changes suggesting ischaemia[17] are also risk factors for cardiac morbidity and mortality.

A number of methods are available to identify patients at high cardiac risk. The commonest method used in the UK was found to be measurement of cardiac ejection fraction[20]. Surgeons who carry out a greater number of vascular procedures were more likely to assess preoperative cardiac risk. The Detsky index is useful in identifying high-risk patients. A score of 10 or more is significantly associated with cardiac morbidity and mortality[5,6]. In this series two-thirds of patients who developed a serious cardiac event had a score of 10 or more.

Bleeding was the cause of death in 20·5 per cent of patients. Serious intraoperative bleeding occurs in approximately 5 per cent of AAA repairs. In half of these patients bleeding arises from the anastomosis or from vascular clamp damage. In the remainder the bleeding comes from major veins[18]. Complications associated with significant intraoperative bleeding include coagulopathy, new cardiac arrhythmias, prolonged ventilation and impaired renal function.

Postoperative chest infection is the commonest cause of morbidity after AAA repair[21]. COAD is a recognized risk factor for mortality[18]. In this series one-third of patients with respiratory failure had severe pre-existing COAD.

Rather than being the cause of death, in the present study MSOF was the 'final common pathway' in the majority of patients who survived the initial complication. Cardiac complications continue to be the main precipitating factor accounting for death after elective aortic reconstruction.

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Survey of changes in the provision of vascular surgical services in the Oxford Region over 5 years

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Aim This study aimed to examine changes in the provision of vascular services in the Oxford region over 5 years.

Methods A questionnaire was sent to all general surgeons in the region asking of their involvement in vascular surgery. Data were obtained from the Department of Health concerning vascular procedures and inpatient codes for each district in the Oxford Region from 1990–1991 to 1994–1995. Office of Population Censuses and Surveys (OPCS) data for abdominal aortic aneurysm repair and femoral artery reconstruction were validated against data collected prospectively for West Berkshire.

Results Eighteen of 45 surgeons who replied to the questionnaire carried out elective and emergency arterial work. All were members of the Vascular Surgical Society of Great Britain and Ireland (VSS). All but one took part in the general surgical rota. Eight surgeons carried out emergency arterial surgery only; only two of these were members of the VSS. Of 19 surgeons undertaking no arterial surgery, 15 operated on primary and 11 on recurrent varicose veins. The number of arterial reconstructions rose from 20·8 per 100 000 population to 28 per 100 000 throughout the study. The greatest increase occurred in districts where a new vascular consultant had been appointed. Similar results were obtained with endovascular procedures. The number of major amputations remained fairly constant at approximately 11 per 100 000 population. The number of inpatient episodes for arterial disease also rose, from 35·7 to 47·6 per 100 000. In validating OPCS codes against prospectively collected data, discrepancies for individual years were noted but the annual trend was reflected fairly accurately by the codes.

Conclusion There has been an increase in vascular activity in the region, but variations still exist between different districts.

The UK is lagging behind Europe in the identification of vascular surgery as a separate subspecialty. A questionnaire survey in 1988 showed that in ten of 21 European countries vascular surgery was separate from both general and cardiothoracic surgery[1]. A survey published in 1992 showed that only 4 per cent of members of the Vascular Surgical Society of Great Britain and Ireland (VSS) were pure vascular surgeons[2].

Nevertheless the general surgical component of vascular and general surgery in the UK is diminishing as vascular surgery expands[3]. This separation is being maintained by the creation of new vascular consultant posts[4].

In a previous report marked differences were identified between hospitals in the Oxford Region in the number of patients admitted with the diagnosis of peripheral vascular disease[5]. A considerable variation was also identified in the number of vascular reconstructions and amputations done. Centres with high rates of distal arterial reconstructions did fewer major amputations. The amputations were likely to be carried out more distally and to have been preceded by a surgical attempt to save the limb[6].

The aim of this study was to determine how the provision of vascular surgery has changed in the Oxford Region over 5 years.

Patients and methods

In 1994 Oxford Region combined with East Anglia to form the Anglia and Oxford Regional Health Authority. This study examines changes in the old Oxford Region between 1990 and 1997. Oxford Region has a population of about 2·5 million. There are eight districts serving populations of 150 000 to 500 000. There is one teaching hospital in the region.

A questionnaire was sent, in February 1997, to each surgeon in the region known to be practising general and/or vascular surgery, asking about involvement in vascular surgery. This was compared with a similar questionnaire from 1992[5].

Data were obtained for inpatient episodes and operations relating to arterial surgery in the Oxford Region. The source for this information was the Department of Health, being based on district statistical returns. Data were obtained for the 5 years from 1990–1991 to 1994–1995. The latter represented the most up-to-date information available. International Classification of Diseases, 9th revision (ICD9) codes obtained were: 441.3–6, 442.0–3, 442.8, 442.9, 444.0–2, 444.8 and 444.9. Office of Population Censuses and Surveys (OPCS) codes relating to vascular procedures and amputations obtained were: L18–20, L29, L34, L37, L41, L45, L48–52, L56–59, L65 and X09. Numbers of patients undergoing iliac (L54.1) and femoral (L63.1) percutaneous transluminal angioplasty (PTA) were also obtained.

Data for West Berkshire District Health Authority were validated against data collected prospectively from the Royal Berkshire Hospital for abdominal aortic aneurysm (AAA) repair (L18, L19) and bypass operations on the femoral artery (L59).

Results

Between 1992 and 1997 six general surgeons with a vascular interest were appointed in the region. Only one of these was to replace a retiring consultant.

Questionnaire study

In the first questionnaire 40 replies were received from 45 surgeons surveyed[5]. In the present study 45 replies were

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received from 47 surgeons. Eighteen surgeons presently carry out emergency and elective arterial surgery, eight do emergency operations only and 19 perform no arterial surgery. These values are similar to those obtained in 1992 (16, 11 and 13 respectively). All the surgeons who carry out emergency and elective arterial work are members of the VSS. In addition to covering vascular surgery, all but one of these 18 surgeons also took part in the general surgical rota. Only two of the eight carrying out emergencies only are members of the VSS. Of 19 surgeons carrying out no arterial surgery 15 undertook primary and 11 recurrent varicose vein operations. Seven of these 19 surgeons stated that they would allow an appropriately trained junior surgeon to carry out an emergency thromboembolectomy under their care. Only one would allow a ruptured aneurysm to be so treated.

Vascular reconstructions

In 1990–1991, 524 operations were carried out in the Oxford Region. This represents approximately 20·8 operations per 100 000 population. By 1994–1995 the number of operations had risen to 701, equivalent to 28 per 100 000 population. *Fig. 1* shows the changes in operations performed for each of the eight districts for 1990–1991 compared with 1994–1995. Excluding the two districts carrying out few reconstructions, the range in the remaining six was 9·2–34·9 in 1990–1991 and 19·1–46·5 in 1994–1995. Each of the three districts to which a new consultant vascular surgeon had been appointed showed an increase in the number of operations done (*Fig. 2*). The mean number of operations in the three districts rose from 14·3 to 28·9 per 100 000. This represents a rise of 102 per cent. In the other five districts there was only a 5 per cent increase in activity (19·2 per 100 000 rising to 20·2 per 100 000).

Amputations

Approximately 11 per 100 000 population major (X09) and minor (X10, X11) lower limb amputations were carried out in the region per year (*Fig. 3*). These figures include amputations for trauma, deformity and malignancy in addition to those carried out for vascular disease. There is not likely to have been any significant change in the first three indications. Of patients referred to the Oxford Region prosthetic service, an original diagnosis of vascular disease (including diabetes) was made in 67 per cent in 1990 compared with 64 per cent in 1996 (J. D. Morrison, personal communication 1997). There appears to be no decrease in the number of amputations despite the increased vascular workload.

Inpatient episodes

Examination of ICD9 codes showed 893 (equivalent to 35·7 per 100 000) inpatient episodes in 1991. By 1994–1995 this had risen to 1190 (47·6 per 100 000), an increase of 33 per cent. The overall increase was greatest in the three districts with a new vascular appointee (50 per cent increase compared with 21 per cent in the other five districts).

Endovascular procedures

The number of iliac and femoral angioplasties performed in the region rose from 8·2 per 100 000 in 1990–1991 to 21·7 per 100 000 in 1994–1995. Excluding two districts that reported no procedures in 1994–1995, the range of procedures in the remaining six districts was 0·7–17·0 in 1990–1991 and 8·1–34·3 in 1994–1995. The three districts in which a new vascular surgeon was appointed showed an

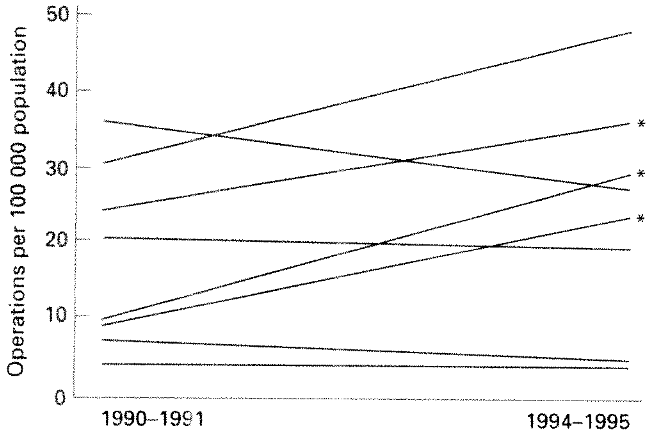

Fig. 1 Number of vascular operations performed in 1990–1991 compared with 1994–1995 for the eight districts. *District with a new vascular consultant appointment

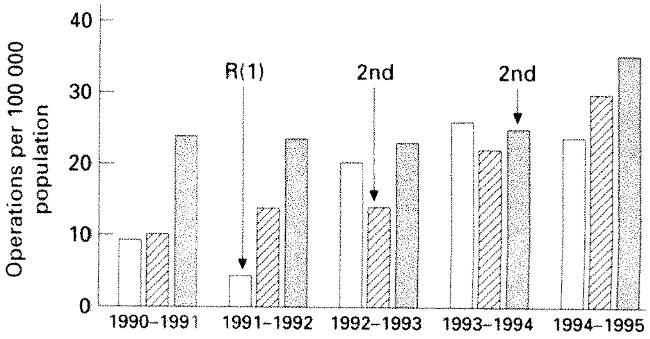

Fig. 2 Number of vascular operations performed in three districts with a new vascular consultant appointment. R(1) shows time of replacement of a single-handed appointment to district □; 2nd indicates timing of new, second, vascular consultants to districts ▨ and ▩

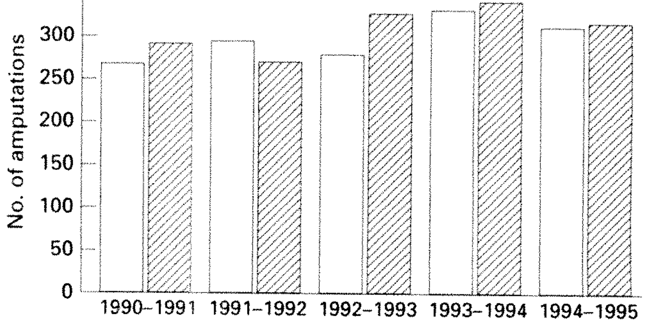

Fig. 3 Number of major (□) and minor (▨) amputations performed throughout the Region

increase of 312 per cent. The increase in the remaining five districts was 268 per cent.

Validation of Office of Population Censuses and Surveys codes compared with prospective audit

There was a close correlation for OPCS codes recorded in West Berkshire compared with the number of aortic aneurysms repaired in the Royal Berkshire Hospital (*Fig. 4*). Some of the variation seen between emergency and elective operations is likely to be due to the fact that acute (non-ruptured) AAAs are not coded separately[7]. Inevitably, therefore, some of these will be included as elective and some as emergency operations. Code L59 is designated 'other bypass of femoral artery'. It includes femorofemoral, femoropopliteal and distal bypass and 'non-specified procedure'. Given the heterogeneous nature of this group it is not surprising that there is more variation when comparing codes with audit. However, the trend showing annual numbers of procedures performed is reflected by the coding (*Fig. 5*).

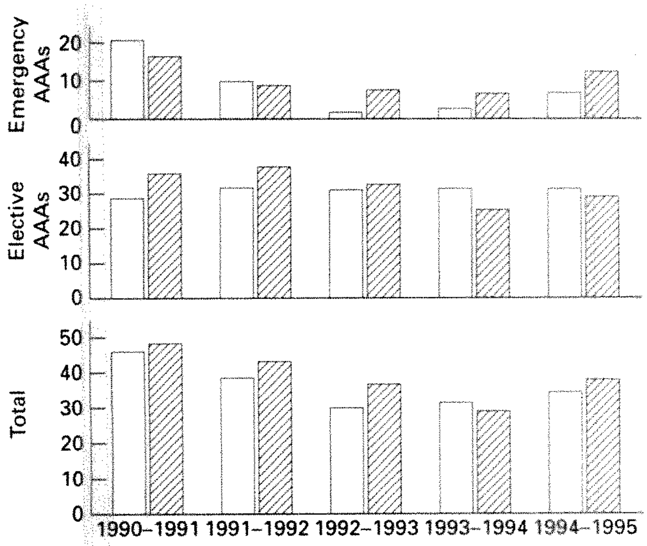

Fig. 4 Number of abdominal aortic aneurysms (AAAs) performed in West Berkshire. □, Office of Population Censuses and Surveys codes for West Berkshire; ▨, Royal Berkshire Hospital vascular surgical audit

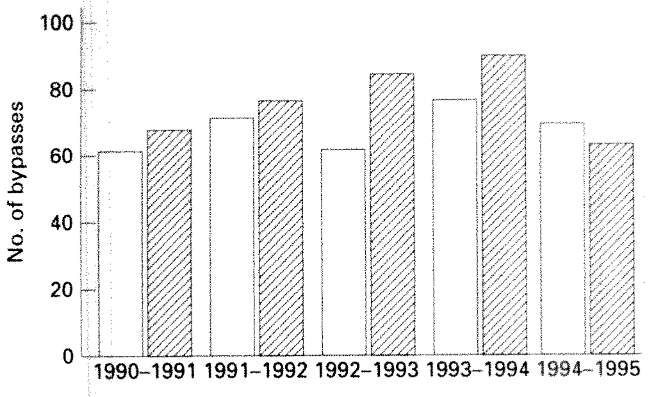

Fig. 5 Numbers of femoral artery bypasses (code L59) performed in West Berkshire. □, Office of Population Censuses and Surveys codes for West Berkshire; ▨, Royal Berkshire Hospital vascular surgical audit

Discussion

ICD and OPCS codes represent a form of statistical analysis of diseases and procedures. Their function is to facilitate the management of healthcare services[8]. They can be regarded as representing an intermediate category between Read codes (comprising clinical terms used most commonly) and Healthcare Resource Group and Health Benefit Groups[9].

ICD and OPCS codes produced by Hospital Activity Analysis have been shown to be up to 20 per cent inaccurate[10]. Furthermore, discrepancies have been identified in the defined codes obtained by different individuals[11]. The present results confirm discrepancies between recorded OPCS codes and data collected prospectively when data are analysed for individual years. However, the trend for change over the 5 years of the study is represented fairly accurately by the coding system (*Figs 4* and *5*).

Analysis of both procedure codes and inpatient episodes for vascular surgery shows an increase in activity over 5 years. These increases were most pronounced for districts in which new vascular surgeons had been appointed. This confirms the findings of others, based on locally collected data, which show increases in vascular activity following both new and replacement consultant vascular appointments[3,12]. The increase in vascular reconstruction and PTA in the region was not associated with any decrease in the number of major amputations, although it has been reported to have reduced the number of amputations in one district of the Oxford Region[13]. Other studies have shown that amputation rates fall as rates of vascular reconstruction and angioplasty rise[6,14]. On the other hand, a large study from Maryland, over 10 years, showed significant increases in the numbers of PTAs and peripheral bypass operations carried out whilst the number of major amputations remained constant[15]. A report from Scotland showed that areas of the country with a high rate of vascular reconstruction had a correspondingly high rate of major amputation[16]. Increasing numbers of vascular reconstructions have, however, been shown to result in an increase in the age of patients having an amputation[17]. It needs to be remembered that not all patients will have a vascular reconstruction for critical ischaemia. Pell *et al.*[16] demonstrated an increase in the number of admissions for patients with peripheral vascular disease, but the number with gangrene who were admitted remained constant. Natural history studies have shown that patients with intermittent claudication have a low risk of developing rest pain or gangrene[18]. However, the quality of life of patients with claudication can be improved by revascularization[19], at least in the short term[20].

The rate of major amputation in the Oxford Region is lower, at approximately 11 per 100000 population, than reported elsewhere. For example, rates of 30 per 100000 have been reported in Denmark[21,22] and 20 per 100000 in Finland[23]. This is not surprising as different rates of atherosclerosis occur in different populations. In Oxfordshire the prevalence of atherosclerosis in a population sample was 2·2 per cent[24]. Values from similar populations in Denmark and rural Finland were 5·8 and 7·7 per cent respectively.

Despite the overall increase in vascular activity across the region, variations in the number of procedures being carried out in different districts are still apparent. Individual surgical units[25] and nationally collected data[26] have shown a steady increase in vascular activity over the past 20 years. Eickhoff *et al.*[27] provided data from the Danish National Patient Register. A statistically significant variation in vascular operations performed in different counties in Denmark was identified. The range of ratios of observed to expected reconstructions was 0·61–1·54.

There is evidence that the general surgical component of a general and vascular surgical firm is falling[3,26]. The majority of vascular surgeons in Oxford Region continue to take part in general surgical emergency cover. It is clear that operations on varicose veins are still regarded as part of general surgery. The majority of surgeons carrying out no arterial operations still dealt with varicose veins, and over half operated on recurrent veins. However, a questionnaire sent by the VSS to members and non-members in 1995 confirmed that, although non-vascular surgeons were carrying out varicose vein operations, they were doing proportionately fewer than in 1992.

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Role of magnetic resonance angiography for assessment of abdominal aortic aneurysm before endoluminal repair

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Background A detailed knowledge of the morphology of the aorta and iliac arteries is an important prerequisite for successful endoluminal abdominal aortic aneurysm (AAA) repair. The best method of preoperative evaluation remains to be determined.

Methods A prospective study was undertaken between January 1994 and July 1995 to assess the ability of computed tomography (CT), magnetic resonance angiography (MRA), colour duplex imaging and intra-arterial digital subtraction angiography (IA-DSA) to visualize AAA morphology.

Results Eighty-two consecutive patients (64 men, 18 women) with AAA were assessed with MRA, contrast-enhanced CT, colour duplex imaging and IA-DSA. Median age was 74 (range 59–87) years and median AAA diameter was 5·7 (range 3·5–9·7) cm. Five patients were unable to tolerate CT or MRA examination. Seventy-seven patients underwent both CT and MRA. Of these, 55 also had a colour duplex scan and 32 underwent arteriography. The scans were assessed by an independent blinded observer. MRA was significantly better ($P < 0·01$) at visualizing AAA morphology compared with CT and colour duplex imaging. There was no statistically significant difference between MRA and arteriography.

Conclusion MRA is useful in patient selection for endoluminal AAA repair, as it avoids use of iodinated contrast medium and ionizing radiation.

For conventional open repair of abdominal aortic aneurysms (AAAs), ultrasonography alone may be adequate for preoperative assessment. Contrast-enhanced computed tomography (CT) or arteriography may be performed if renal artery involvement or associated distal arterial occlusive disease is suspected[1]. Endoluminal AAA repair, however, requires a more detailed assessment of the abdominal aorta for determining patient suitability and accurate sizing of the intraluminal prosthesis[2].

Neither CT nor arteriography is completely reliable in predicting the proximal or distal extent of AAA[3,4]. Some of the drawbacks can be overcome with spiral CT[5], although the problems of X-ray exposure and injection of iodinated contrast media persist. A major drawback of angiography is that, in the presence of mural thrombus, the external extent of the AAA sac is not visualized.

Recent studies using magnetic resonance angiography (MRA) suggest that this may be a better tool for assessing AAA morphology[6–8] than conventional cross-sectional imaging. Previously spin-echo magnetic resonance imaging (MRI) provided only limited detail of the aortic branch vessel anatomy. However, the development of MRA using gradient echo techniques combined with contrast enhancement (*Fig. 1*) has overcome many of these limitations[8,9].

In this study an assessment was made of the ability of CT, MRA, colour duplex imaging and intra-arterial digital subtraction angiography (IA-DSA) to visualize AAA morphology.

Patients and methods

Patients with asymptomatic AAAs referred to Leicester Royal Infirmary between January 1994 and July 1995 underwent assessment with MRA, contrast-enhanced CT and colour duplex imaging. Those with favourable anatomy for endoluminal repair on the basis of these three non-invasive imaging modalities underwent further assessment with IA-DSA. The ability of each test to visualize the following parameters was determined: right and left renal artery origin, proximal aneurysmal neck length, maximum anteroposterior diameter, tortuosity of aneurysm sac,

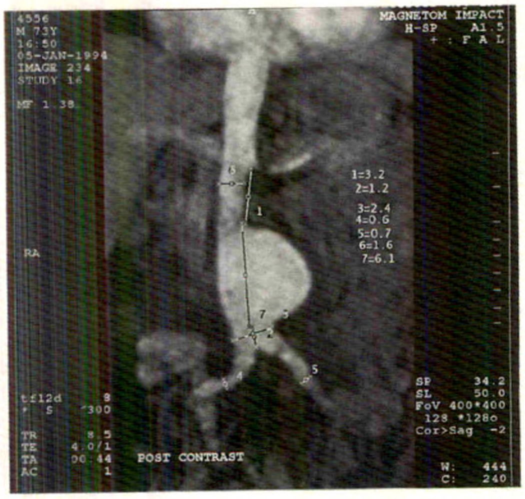

Fig. 1 Image of the abdominal aorta obtained using magnetic resonance angiography (gradient echo sequence), demonstrating the origin of the renal arteries, the infrarenal abdominal aortic aneurysm and tortuosity of the iliac arteries

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distal neck length, tortuosity of iliac arteries and iliac artery diameter. The proximal neck was defined as the non-aneurysmal segment of aorta (less than 30 mm) between the origin of the lowest renal artery and the start of the aneurysm (aortic diameter greater than 30 mm), and the distal neck was defined as the length of non-aneurysmal segment before the aortic bifurcation.

Magnetic resonance angiography

All scans were performed on a Siemens (Erlangen, Germany) IT scanner employing 10mT/m gradients and a 50-cm body coil. A rapid magnetization prepared two-dimensional, gradient echo multiplanar sequence (TurboFLASH-time to repetition 8.5, echo time 4, inversion time 300, flip angle 8, 128 × 128, field of view 400 × 400, 8 mm thick) was used. Four discrete blocks of slices were positioned to acquire images directly in the coronal and sagittal planes and obliquely along the line of the renal arteries. Contrast enhancement was achieved using intravenous injection of 15 ml of gadolinium diethylenetriamine penta-acetate (Magnevist; Schering, Burgess Hill, UK) diluted to 30 ml with normal saline. The contrast injection was timed to allow a precontrast measurement, one during the arterial phase, one in the venous phase and a final steady-state measurement. All scans were obtained during quiet respiration. The total scanning time was 3 min. Images were viewed either from the source images or were postprocessed using maximum intensity projection to create angiographic type images in each of the four planes: coronal, sagittal and two paraoblique. Postprocessing on average took 20–30 min.

Computed tomography

CT was performed using a Siemens HiQ scanner. Contiguous slices of 10 mm thickness were obtained from the diaphragm inferiorly. On reaching the renal vessels 3-mm slices were used, and a similar scanning technique was employed through the region of the aortic bifurcation. The intervening aorta was scanned with 10-mm slices. Some 100 ml of contrast (Omnipaque 320; Nycomed, Birmingham, UK) was hand-injected at approximately 2 ml/s when scanning from the level of the renal vessels, which was performed dynamically in quiet respiration and commenced after a 40-s delay.

Colour duplex imaging

Colour duplex examinations were performed with an Advanced Technology Laboratories Ultramark-9 HDI colour scanner (Advanced Technologies, Washington, DC, USA). All examinations were performed by an experienced vascular technician using a colour Doppler imaging frequency of 3·0 MHz and a pulsed Doppler frequency of 2·5 MHz.

Intra-arterial digital subtraction angiography

IA-DSA was performed by percutaneous catheterization of the femoral artery using the Seldinger technique. A marker pigtail catheter with eight side-holes (6 Fr, 65 cm long; Cordis, Miami, Florida, USA) was used. Some 80 ml of contrast (Omnipaque 300; Nycomed) were injected at 20 ml/s. Anteroposterior and lateral views of the abdominal aorta, and anteroposterior and oblique views of the iliac arteries, were obtained with a Siemens Multiskop equipped with a Digitron computer system (Siemens).

Results

A total of 82 patients was assessed. There were 64 men and 18 women of median age 74 (range 59–87) years. Median AAA diameter was 5·7 (range 3·5–9·7) cm. Five patients did not tolerate CT ($n = 1$) or MRA ($n = 4$) and were excluded from analysis.

Table 1 Comparison of aneurysm morphology visualized by each investigation

Parameter	CT	MRA	Colour duplex	IA-DSA
Right renal artery	64	91	51	100
Left renal artery	78	97	51	100
Proximal neck length	80*	95	51	78
Maximum anteroposterior diameter	100	100	98	6
AAA sac tortuosity	0	100	94	97
Distal neck length	92	99	94	59
Tortuosity of iliacs	0	91	85	100
Diameter of iliac arteries	91	84	78	100

Values are the percentage of patients in whom each parameter was visualized adequately. *In some patients this measurement was inferred from visualization of a single renal artery origin. AAA, abdominal aortic aneurysm; CT, computed tomography; MRA, magnetic resonance angiography; IA-DSA, intra-arterial digital subtraction angiography

Comparison of imaging techniques

Seventy-seven patients successfully underwent both CT and MRA. Of these, 55 also had a colour duplex scan and 32 proceeded to IA-DSA. The scans were assessed by an independent blinded observer. The results are presented as the percentage of patients in whom the above parameters could be assessed adequately by each investigation (*Table 1*).

Visualization was considered to be adequate if six or more parameters (from a maximum of eight) were identifiable. Statistical analysis using the χ^2 test showed MRA (95 per cent adequate) to be significantly better ($P<0{\cdot}01$) at visualizing AAA morphology than CT (50 per cent) and colour duplex imaging (45 per cent). There was no statistically significant difference between MRA and IA-DSA (95 *versus* 85 per cent respectively).

Aortic aneurysm morphology

On the basis of the above results, MRA images in 78 patients were used to study AAA morphology and to determine suitability for endoluminal repair. Four distinct morphological groups were identified when applying the current criteria for endoluminal repair (*Table 2*): group 1 – aneurysms with a sufficient proximal and distal neck ($n = 21$); group 2 – aneurysms with a sufficient proximal

Table 2 Anatomical criteria used currently for endoluminal abdominal aortic aneurysm repair with tube and bifurcated grafts

	Tube	Bifurcated
Proximal neck length (mm)	15	15
Proximal neck diameter (mm)	<28	<28
Distal neck length (mm)	10	0
Iliac artery diameter (mm)		
Minimum	8	8
Maximum	—	14

Severe aneurysm and iliac artery tortuosity (change in direction greater than 60°) also contraindicate endoluminal repair

Table 3 Reasons for unsuitability for endovascular abdominal aortic aneurysm repair

	No. of patients ($n = 78$)
Group 1 ($n = 21$)	
Suitable for tube or straight graft	12 (15)
Unacceptable proximal neck or iliac angulation	4 (5)
Distal neck stenosis	1 (1)
Isolated iliac aneurysms	3 (4)
Proximal neck diameter greater than 28 mm	1 (1)
Group 2 ($n = 37$)	
Suitable for bifurcated graft endoluminal repair	16 (21)
Proximal neck diameter greater than 28 mm	2 (3)
Iliac artery stenosis less than 7 mm	2 (3)
Unacceptable proximal neck or iliac angulation	5 (6)
Extension of aneurysm to internal iliac artery (greater than 14 mm)*	12 (15)
Group 3 ($n = 14$)	
Insufficient proximal neck length (less than 15 mm)	14 (18)
Group 4 ($n = 6$)	
Pararenal or suprarenal aneurysm	6 (8)

Values in parentheses are percentages. *May be treated with an aortouni-iliac graft in combination with femorofemoral crossover bypass

neck but insufficient distal neck or iliac involvement ($n = 37$); group 3 – infrarenal aneurysms with insufficient proximal neck ($n = 14$); and group 4 – aneurysms with pararenal or suprarenal extension ($n = 6$).

Overall only 28 patients (36 per cent) met the criteria for endovascular repair. Of the 21 patients in group 1, only 12 were suitable for a straight or tube graft. A further three patients from group 1 could be treated with a tube graft in combination with endoluminal repair of an isolated common iliac aneurysm. Of the 37 patients in group 2, only 16 met the criteria for a bifurcated endoluminal graft. *Table 3* lists the reasons for excluding other patients from endoluminal repair. There was no significant correlation between the size of the aneurysm and the length of the proximal and distal necks.

Discussion

Vascular imaging plays a vital role in determining patient suitability for endoluminal AAA repair and in the selection of an appropriate endovascular device[10,11]. Although conventional CT remains useful in prediction of AAA size and detection of other retroperitoneal pathology[12], it has several drawbacks. The visceral and renal artery origins are often not visualized, as they may fall between slices, and have to be inferred from the surrounding anatomy[13]. Conventional CT images are obtained along the axial plane of the body which does not conform to the plane of the aortoiliac segment as it is often angulated and tortuous in patients with AAA. This produces oblique images of the aorta making interpretation of visceral artery origins difficult. It is not possible to obtain assessment of the proximal neck length in these cases, which is an important factor in determining patient suitability for endoluminal repair. In this study there was inadequate visualization of both renal artery origins in up to 40 per cent of patients. Visualization of the renal arteries was considered adequate only if their origin from the aorta was seen clearly on a scanning plane. Adherence to this strict criterion may account for the above poor results. Conventional CT also results in potential inaccuracies in assessment of the aneurysmal sac length and tortuosity of the aortoiliac segment.

Colour duplex scanning has been proposed previously as the modality of choice for preoperative assessment of AAA for endoluminal repair[14]. In this centre, although colour duplex is regarded as a 'gold standard' for assessment of lower limb arterial lesions[15], it is not as useful in the assessment of AAA. It provided excellent assessment of the distal extent of the aneurysm and of the iliac artery morphology but in around 50 per cent of patients visualization of the renal artery origins was obscured by the presence of bowel gas or obesity. Duplex imaging is, however, very operator dependent and therefore results may vary between centres[14].

Arteriography is very useful in demonstrating visceral artery origins and for assessing the state of the distal vessels[16,17]. However, in the presence of mural thrombus, the proximal and distal limits of the aneurysm sac are obscured, and the normal calibre of the lumen may be mistaken for normal aorta, with overestimation of the proximal and distal neck lengths. Another important limitation of aortography is that of magnification error. This may partially be overcome by use of a calibrated angiographic catheter (as described above) but accurate assessment of arterial diameters is still difficult.

MRA has evolved to become an accepted non-invasive method of imaging arteries[18–21]. MRA uses gradient echo techniques to create angiographic type images which may be acquired using two-or three-dimensional techniques. It is not affected by bowel gas and can outline the size of the lumen as well as the thrombus thickness without the use of iodinated contrast medium. The disadvantages of MRA are relatively few. A small proportion of patients experience claustrophobic symptoms and may not tolerate the examination (5 per cent in this study). MRA is also contraindicated in patients with pacemakers or intracranial metal clips. The entire examination can be completed in 20–30 min. Image quality and scan acquisition times continue to be improved by technical advances such as improved gradient strengths and local coil design. In conjunction with bolus-technique contrast enhancement, this results in high-resolution, high-contrast, relatively artefact-free angiographic type images. In the present study MRA provided the best non-invasive assessment of the AAA parameters relevant to patient selection and graft sizing for endoluminal repair.

In this study only 36 per cent of patients could be treated endoluminally with the currently available tube and bifurcated devices, consistent with other series[5,22,23]. A tapered aortouni-iliac graft with occlusion of the contralateral common iliac artery and an extra-anatomic crossover graft can be used when the iliac vessels are wide (greater than 14 mm) or aneurysmal. This device is, therefore, applicable in a higher proportion of patients but doubts remain about the long-term patency of the extra-anatomic bypass[24]. A significant proportion of patients continue to require conventional open repair.

MRA could have a role in patient selection for endoluminal repair and can produce the same information as combined CT and aortography but without the use of iodinated contrast medium, ionizing radiation or arterial puncture. Conventional angiography can, therefore, be reserved for patients who require distal artery imaging.

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A 21-year experience of abdominal aortic aneurysm operations in Edinburgh

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Background This study reviews the results of infrarenal abdominal aortic aneurysm (AAA) surgery over 21 years (1 January 1976 to 31 December 1996).

Methods A prospectively gathered database was analysed.

Results Infrarenal AAA repair was performed in 1515 patients: 492 (32·5 per cent) had elective repair of an asymptomatic AAA; 194 (12·8 per cent) had elective repair of a symptomatic AAA; 156 (10·3 per cent) had emergency repair of a symptomatic non-ruptured AAA; and 673 (44·4 per cent) had surgery for a ruptured AAA. The 30-day and/or same admission mortality rates were 6·1, 5·8, 14·1 and 37 per cent respectively. Operative mortality increased in all four groups over the study interval, although this only attained statistical significance in patients having elective repair of a symptomatic, non-ruptured AAA. There was a significant increase in the age of patients undergoing elective repair of an asymptomatic AAA, but not in the other three groups. There was also a significant increase in the proportion of straight 'tube' grafts inserted in all four groups.

Conclusions It remains the minority of patients who have elective operation before the onset of symptoms and/or rupture. Despite anaesthetic and surgical specialization, the results of AAA repair have not improved over the past two decades. Operative mortality may be increasing, possibly because of the increasing age and associated comorbidity of the patients presenting to this unit.

In the UK, infrarenal abdominal aortic aneurysm (AAA) more than 4·0 cm in diameter occurs in 2·3 per cent of men aged 65–74 years, and is estimated to be responsible for death in 1·7 per cent[1]. The number of patients with AAA presenting to vascular surgeons is increasing because of the growing awareness of the condition, more widespread use of abdominal imaging, ageing of the population and, possibly, increasing prevalence of the condition[2,3].

Operative series published from North America and Australasia suggest that the mortality rate associated with elective AAA repair is falling, and may even approach zero[4–6]. National[7] and local[8] audit data suggest that this is not the case in most UK hospitals and that elective mortality may, not infrequently, approach double figures[9].

By contrast, most accept that the mortality associated with repair of a ruptured AAA has failed to improve. Aneurysms at significant risk of rupture should therefore be identified and repaired wherever possible. In the UK, the number of asymptomatic AAAs currently detected and repaired is too small to affect significantly the overall community mortality from rupture. Whereas in the USA the ratio of elective to emergency repairs is increasing[10] and may be as high as 10:1, in the UK the reported ratio is often less than 2:1 and shows no sign of increasing[11,12]. The current management of AAA in the UK may be far from satisfactory, and is perhaps failing to improve in line with other countries where healthcare resources are more plentiful. The aim of the present study was to review the pattern of presentation and the results of AAA surgery in this unit over 21 years to determine whether any progress had been made in the management of this condition.

Patients and methods

A prospectively gathered database containing demographic, clinical, operative and outcome data on all patients who had surgery for infrarenal AAA in Edinburgh Royal Infirmary between 1 January 1976 and 31 December 1996 was analysed. Operative mortality was defined as death within 30 days of surgery or during the same admission as the operation. A patient was deemed to have undergone an AAA operation if he or she had received an anaesthetic with the intention of repairing the AAA, whether a graft was successfully inserted or not. Patients treated without surgery are not reported in this series. Data from 1976 to 1982 represent the work of three consultants with a special interest in vascular surgery who combined formally to create the Edinburgh Regional Vascular Surgery Unit in 1983. Throughout most of the study the unit has been staffed by three consultants, a fourth was appointed in October 1996. The population served in southeast Scotland approaches 1·2 million and has remained relatively constant during the study.

Results

A total of 1515 patients had surgery for an infrarenal AAA: 492 (32·5 per cent) had elective repair of an asymptomatic AAA; 194 (12·8 per cent) had elective operation for a symptomatic non-ruptured AAA; 156 (10·3 per cent) had emergency surgery for a symptomatic non-ruptured AAA; and 673 (44·4 per cent) had surgery for a ruptured AAA (*Fig. 1*). The operative mortality rates were 6·1, 5·8, 14·1 and 37·0 per cent respectively.

The proportion of patients who had elective repair did not significantly increase during the study. The male:female ratio did not change significantly during the study in any clinical group. Patients who had repair of a ruptured AAA were less likely to be female (119 of 673, 17·7 per cent) than those who had repair of a non-ruptured AAA (190 of 842, 22·6 per cent) ($P = 0{\cdot}02$,

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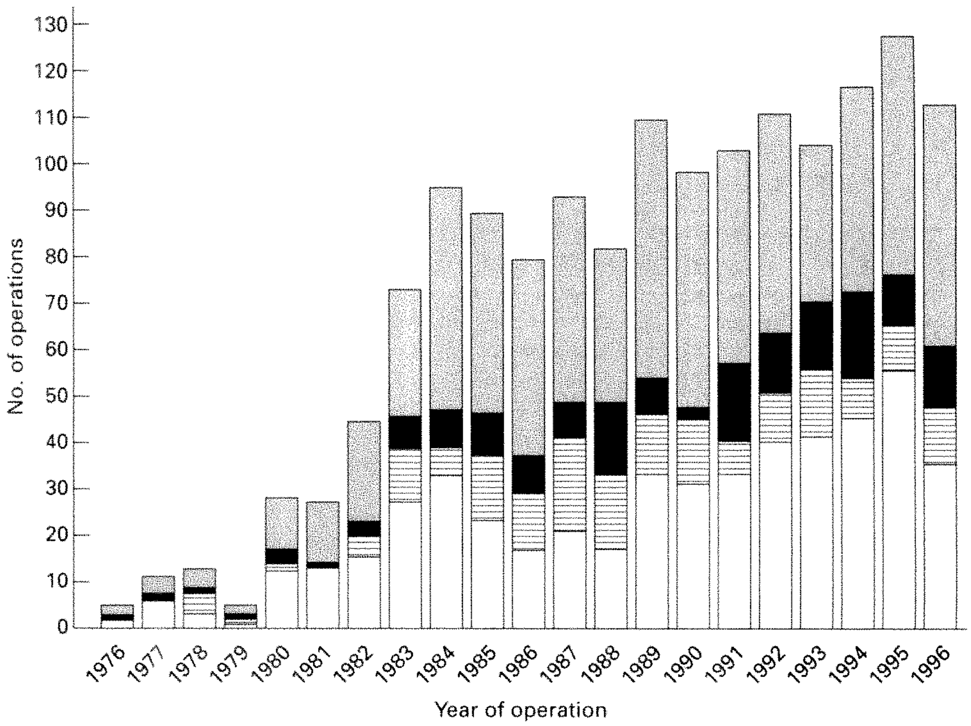

Fig. 1 Number of, and indication for, abdominal aortic aneurysm repair between 1976 and 1996. □, Asymptomatic; ▤, symptomatic elective; ■, symptomatic emergency; ▨, rupture

Fisher's exact test). The sex ratio was not significantly different between the three non-rupture groups.

Operative mortality increased in all groups, but this only attained statistical significance in patients who had elective surgery for a symptomatic, non-ruptured AAA ($P<0{\cdot}008$, χ^2 test) (*Fig. 2*). There was a significant increase in the proportion of tube grafts inserted in all groups ($P<0{\cdot}01$, χ^2 test) (*Fig. 3*). Mortality was lower in patients who had repair with a tube graft (119 of 767, 15·5 per cent) compared with a bifurcated graft (118 of 648, 18·2 per cent), although this difference did not attain statistical significance. Sixty-seven patients with a ruptured aneurysm did not have a graft inserted successfully and all died in the operating theatre. There was a tendency for women having an aneurysm repair to be older than men, although this only attained statistical significance in patients with a ruptured aneurysm ($P<0{\cdot}04$, Mann–Whitney U test). In all groups, median age of the patients increased over the study interval, but this difference was significant only in those who had elective repair of an asymptomatic AAA ($P<0{\cdot}001$, χ^2 test) (*Table 1*). There was no significant association between age and outcome in patients undergoing repair of a non-ruptured AAA. However, in patients with a ruptured AAA 158 of 376 (42·0 per cent) aged over 70 years died compared with 91

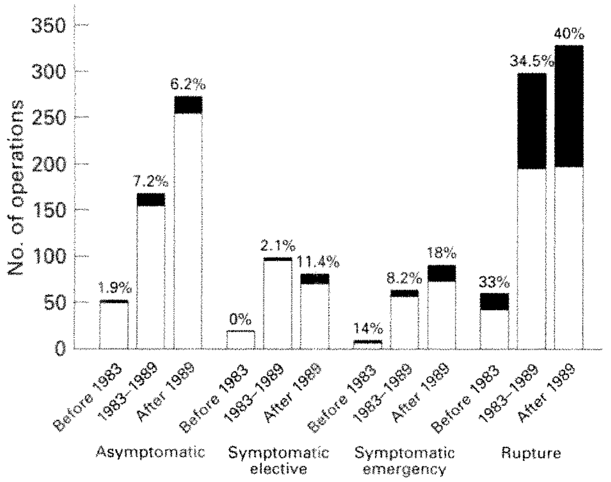

Fig. 2 Indication and time interval for mortality rate following abdominal aortic aneurysm repair. □, Survivors; ■, non-survivors

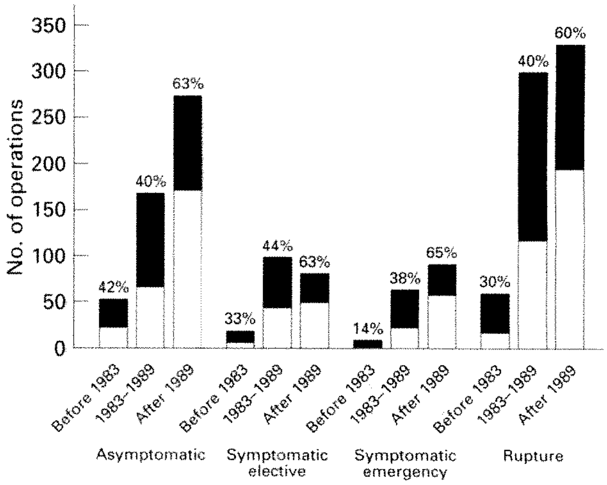

Fig. 3 Indication and time interval for type of graft inserted at abdominal aortic aneurysm. □, Tube graft; ■, bifurcated graft

Table 1 Age of patients undergoing AAA repair by indication and time interval

	1976–1982	1983–1989	1990–1996	P
Age (years)				
Asymptomatic	67 (51–77) (64–72)	68 (48–81) (63–73)	71 (44–75) (66–75)	$<0{\cdot}01$
Symptomatic elective	67 (54–77) (57–69)	68 (43–84) (62–73)	69 (49–86) (63–74)	0·21
Symptomatic emergency	69 (54–78) (61–75)	71 (54–84) (63–75)	72 (49–89) (66–78)	0·19
Rupture	70 (43–86) (63–74)	72 (51–84) (67–76)	71 (52–86) (66–76)	0·11

Values are median (range) (interquartile range)

of 297 (30·6 per cent) aged 70 years or less ($P = 0{\cdot}003$, Fisher's exact test).

Discussion

The first principal finding is that, despite increasing surgical and anaesthetic specialization and experience, there has been no measurable improvement in the outcome of surgery for AAA over the past two decades, regardless of indication or degree of urgency. Indeed, operative mortality has tended to increase. Disappointingly, it is still the case that only a minority of patients in Edinburgh have elective surgery before the onset of symptoms and/or rupture. Although the pressure to publish only good or improving results must not be forgotten[13], the Edinburgh experience may reflect UK practice and appears to differ significantly from that reported in other developed countries. The results of any operative series depend crucially upon case mix. Published reports cannot be compared directly unless they contain detailed information with regard to catchment area and population, referral patterns, selection policies, patient risk factors, and the proportion and characteristics of patients refused operative repair. These in turn are difficult to define with precision and almost inevitably change over time. In the present series, there was a tendency for mean patient age to increase with time in all clinical groups, although this only attained statistical significance in patients having elective repair of an asymptomatic AAA. It is the clinical impression that the number of patients referred with large, surgically unfavourable AAA, and significant multisystem comorbidity, has increased markedly in recent years. At the same time, a recent local audit has indicated that a significantly greater proportion of referred patients with aneurysm rupture are accepted for surgery than was the case 5–10 years ago[12]. Despite deteriorating access to high dependency and intensive care beds locally it is becoming more difficult to turn down high-risk patients for either elective or emergency aneurysm repair, often due to pressure from families or medical colleagues. Although these factors may, at least in part, explain why the overall operative mortality has not decreased, it is difficult to prove. The fact that there has been a tenfold increase in AAA workload with little increase in resources and none in personnel may be equally relevant. Unless in future, patients are identified at an earlier stage, surgeons are unlikely to make a significant impact on overall community mortality from aneurysmal disease.

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Population-based record linkage study of the incidence of abdominal aortic aneurysm in Western Australia in 1985–1994

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Background The incidence of abdominal aortic aneurysm (AAA) has increased steadily during the past 30 years.

Methods Trends in the incidence and surgical intervention for AAA in Western Australia were reviewed for the interval 1985–1994. A population-based health database was used to link morbidity and mortality records of all patients aged 55 years or more who died from rupture or were admitted and treated surgically for AAA. Three groups were separated for analysis: patients with a ruptured AAA, those admitted for elective repair and those admitted as an emergency with an acute (non-ruptured) aneurysm.

Results There was a decline in the incidence of both emergency and elective procedures for AAA after 1992. While the mortality rate from ruptured AAA has also fallen since 1991, the overall case fatality rate for ruptured AAA has fallen by only 1·3 per cent (from 80·7 to 79·3 per cent).

Conclusion The decline in mortality rate and emergency procedures may result from a fall in the incidence of ruptured AAA, due to an increasing rate of elective surgery before 1992. The decline in elective procedures from 1992 may be due to a fall in the prevalence of AAA owing to high rates of elective surgery, or to a fall in the incidence of the disease itself.

The rate of elective surgery for abdominal aortic aneurysm (AAA) has increased steadily over the past 30 years[1–5]. This trend has been driven by an improved awareness of the disease, an increased diagnostic rate and the expectation that elective surgery would result in a fall in the incidence of ruptured AAA. However, the incidence of aneurysm rupture between the late 1970s and the early 1990s, and the overall age-standardized mortality rate from AAA, have risen[1–3,5–7]. This rise has generally been attributed to an increase in the incidence of AAA associated with an inadequate diagnostic rate for asymptomatic AAA in an ageing population. There is considerable interest, and controversy, in the role of population screening as a means of reducing the mortality rate from AAA[8–10].

On the basis of anecdotal observations that the number of ruptured AAAs in Western Australia appeared to have fallen over recent years, a review was carried out of the trends in operations for AAA and deaths from AAA in Western Australia between 1985 and 1994.

Patients and methods

Western Australia Health Services Research Linked Database

The Western Australia Linked Database was established in 1995 and currently collates 16 years of inpatient hospital morbidity data, birth and death registrations, midwives' notifications, mental health services data and notifications to the cancer registry. These data constitute around 8 million records and include all hospital admissions and readmissions to public and private hospitals in the State.

Linkage between the six core data sets is based on six Automatch passes with unit medical record number (specific among all metropolitan teaching hospitals, and within all other hospitals), surname, forename, initial, date of birth, sex and address as the principal matching fields. The Western Australia Linked Database has been structured using a chain of links method, which enables the state of linkage between records to be reconstituted as it was found on any previous date. Validation can be performed manually where necessary for any verification required. To protect the confidentiality of patient information a de-identified version of the Linked Database is used for all research purposes. The de-identification process replaces all patient identification data with a unique number.

For this study the morbidity records of all patients readmitted for AAA or dying from rupture before admission in Western Australia were linked for the interval 1985–1994. As the linkage of 1995 mortality data was not complete, additional 1995 data were obtained from the State Health Department and are included in *Fig. 1*.

All patient morbidity records before 1988 were selected using the combined International Classification of Diseases (ninth revision) (ICD9) diagnosis codes (441.30 or 441.40)[11] or International Classification of Procedures in Medicine procedure code (58.53)[12]. Patients admitted from 1988 to 1994 were selected using the combined ICD9-CM diagnosis codes (441.30 or 441.40)[13] or ICD9-CM procedure code (38.44)[14]. Three groups were separated for analysis: patients with 'rupture', those admitted for 'elective' repair and those admitted to hospital with an 'acute aneurysm' (admitted as an emergency without mention of rupture and who underwent repair for AAA). To allow the overall case fatality rate from rupture to be determined within the State, patients with a ruptured aneurysm were further divided into three subgroups: those who died before admission to hospital (based on the primary cause of death as recorded in the State death records), those who were admitted but not

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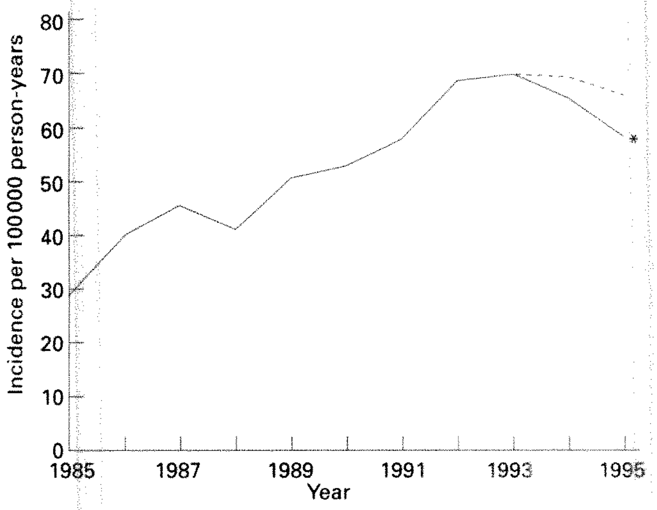

Fig. 1 Age-standardized total (men and women) annual incidence rates of open repair for abdominal aortic aneurysm. Endoluminal stent grafting (ELG) was commenced in 1993. ———, Excluding ELG; -----, including ELG. *1995 incidence estimate obtained from the Health Department of Western Australia

treated surgically and those who were admitted and had aneurysm repair. Selection was restricted to patients aged 55 years and over as cases of AAA under this age were rare (less than 2 per cent of cases) and may be atypical[15]. Data concerning all patients who died from AAA without being admitted to hospital for the study interval 1985–1994 were obtained from the Western Australia Death Register using the ICD9 death code 4413 as coded by the Australian Bureau of Statistics. The de-identified linked research database was current on the 20 November 1996.

All patients admitted with an acute aneurysm underwent operation. In 241 patients (93·8 per cent) this was the primary diagnosis and procedure; the remaining 16 (6·2 per cent) included patients with a variety of other diagnoses (and consequently procedures) including renal cell carcinoma, renal artery stenosis and acute distal occlusive peripheral vascular disease. The only basis for distinguishing these patients in this study was emergency admission. Although some reports include these with elective cases (i.e. a non-rupture group), they were analysed separately in this study as they are different with respect to co-morbidity[16–18].

A specific code for the procedure of endoluminal stent grafting of AAA had not been established. As all these procedures were performed exclusively in one vascular unit (Royal Perth Hospital), accurate data on procedure numbers were available and have been incorporated into *Fig. 1*, but not into subsequent figures.

The index admission for each patient was defined as the hospital admission in which the repair procedure was first carried out. Annual age-standardized and age-specific procedure and mortality rates per 100000 person-years for those aged over 55 years were estimated using the direct method of age standardization[19] and the World Standard Population as the standard set of weights[20]. Men and women were analysed separately. Population estimates were obtained from the Australian Bureau of Statistics (Catalogue 3203.5) and were used as denominators for the calculations. Census population data for 1994 were not available, so estimates were calculated by linear regression using data from the previous 5 years.

In addition to the annual age-standardized and age-specific rates, the crude operative (30-day) mortality rate for patients admitted with aneurysm rupture, acute aneurysm and elective repair was calculated using operation numbers for each category as the denominator (*Table 1*). The total case fatality from rupture was calculated using the total number of ruptured AAAs as the denominator (*Table 2*). As there was considerable annual variation in these rates, the data were grouped into two 5-year intervals to show trends. Differences between the two intervals were evaluated with the χ^2 test with Yates' correction.

Table 1 Crude operative mortality rate at 30 days in men and women admitted for rupture, acute aneurysm and elective repair

	1985–1989	1990–1994	Total	P†
Rupture repair				
Patients	128	155	283	
Deaths	55 (43·0)	47 (30·3)	102 (36·0)	0·04
Acute aneurysm repair				
Patients	157	100	257	
Deaths	16 (10·2)	7 (7·0)	23 (8·9)	0·52
Elective repair				
Patients	250	685	935	
Deaths	12 (4·8)	28 (4·1)	40 (4·3)	0·77
Total repair				
Patients	535	940	1475	
Deaths	83 (15·5)	82 (8·7)	165 (11·2)	$<0·001$

Values in parentheses are percentages, calculated using the number of operations as the denominator. Endoluminal stent grafts ($n = 13$) are not included. †1985–1989 *versus* 1990–1994 (χ^2 test)

Table 2 'Total case fatality' from ruptured abdominal aortic aneurysm in Western Australia showing the contributions of deaths before admission to hospital and following admission with and without surgery

Ruptured AAA	1985–1989 ($n = 379$)	1990–1994 ($n = 494$)	Total ($n = 873$)	P*
Death without admission	171 (45·1)	208 (42·1)	379 (43·4)	0·41
Admitted, death without surgery	80 (21·1)	131 (26·5)	211 (24·2)	0·08
Operative death (within 30 days)	55 (14·5)	47 (9·5)	102 (11·7)	0·03
Total mortality	306 (80·7)	386 (78·1)	692 (79·3)	0·39

Values in parentheses are percentages. AAA, abdominal aortic aneurysm. *1985–1989 *versus* 1990–1994 (χ^2 test)

Results

Between 1985 and 1994, there was a 20 per cent increase (from 1·42 to 1·70 million) in the overall population of Western Australia and a 25 per cent increase (to 307088) in the number of people aged 55 years or more. The increases in the number of men and women aged 55 years or over were similar (26 and 25 per cent respectively). A total of 1475 open repairs for AAA were identified in 1985–1994, of which 85·2 per cent were in men and 14·8 per cent were in women (male to female ratio of 5·8:1). A further 183 open repairs were documented in 1995 (included in *Fig. 1* only). Of all aneurysm repairs performed in Western Australia between 1985 and 1994, 283 (19·2 per cent) were for rupture, 935 (63·4 per cent) were elective and 257 (17·4 per cent) for acute aneurysm repair (*Table 1*). This does not include endoluminal stent grafting, which was introduced at a single institution: two cases in 1993, 11 in 1994 and 24 in 1995.

Procedure rates

A substantial increase (from 27·4 per 100 000 to 70·8 per 100 000 person-years) in the total age-standardized annual incidence rate of open repair for AAA occurred between 1985 and 1993 (*Fig. 1*). After the peak rate of 70·8 per 100 000 person-years in 1993, it fell by around 18 per cent (to 58·2 per 100 000 person-years) in 1995. A small temporary decline of around 8 per cent was observed in 1988, which corresponds to the time at which the coding classification changed from ICD9 to ICD9-CM. The greatest contribution to the changes in the total annual incidence rate was an increase in the number of men undergoing elective surgical repair (*Fig. 2a*).

There was an increase in the age-specific incidence rate of AAA in men of all age groups between 1985 and 1992, after which a decline occurred in all age groups except those aged 65–69 and 75–79 years. The data reflect the general trends seen in *Fig. 1* and show that AAA is uncommon in men aged 55–59 years (mean age-specific rate of 15·7 per 100 000 person-years). The incidence increases steadily to a maximum incidence rate in those aged 75–79 years (mean age-specific rate of 150·6 per 100 000 person-years), and then declines in those aged 80 years or more (mean age-specific rate of 100·2 per 100 000 person-years).

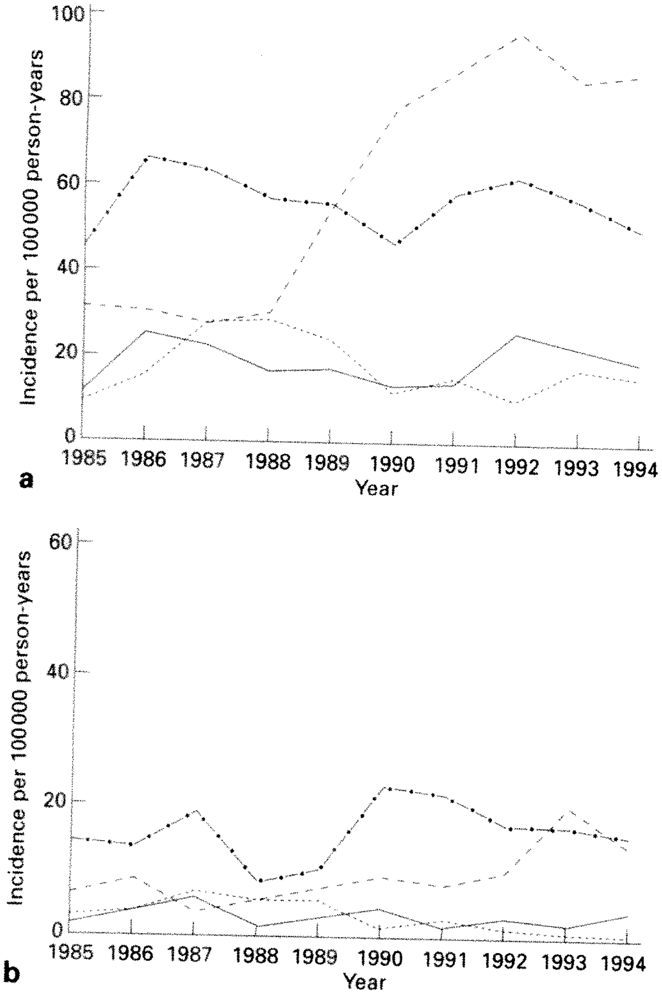

Fig. 2 Age-standardized annual incidence rates in **a** men and **b** women with rupture repair (———) (including those who died without surgery (——·——·——)), and those admitted for acute aneurysm repair (······) and elective repair (— — —)

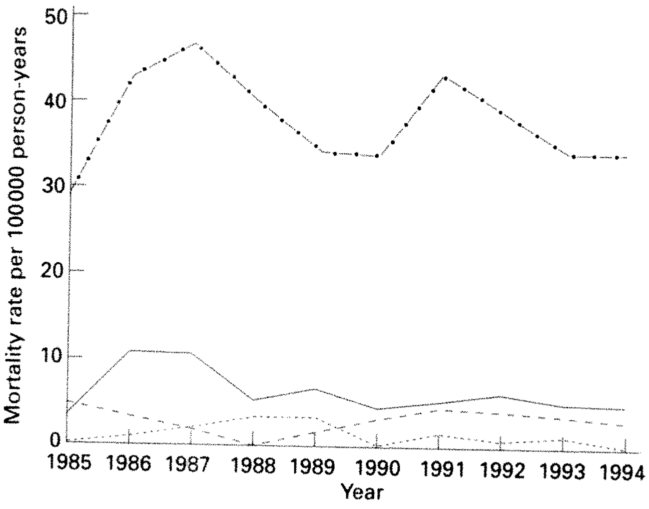

Fig. 3 Age-standardized annual mortality rate from abdominal aortic aneurysm in men with rupture repair (———) (including those who died without surgery (——·——·——)) and those who died within 30 days of admission for acute aneurysm repair (······) and elective repair (— — —)

Mortality rates, operative mortality and case fatality

The age-standardized mortality rate for rupture in men varied considerably during the study (*Fig. 3*), in general reflecting the incidence of rupture (*Fig. 2a*). A similar pattern was seen in women (data not shown). Postoperative deaths after elective and acute aneurysm repair added little to the total mortality rate and there was no obvious trend over time.

The crude operative (30-day) mortality rate after surgery for rupture, acute aneurysm and elective repair is summarized in *Table 1*. Case mortality from rupture including cases not admitted to hospital is summarized in *Table 2*. Although the operative mortality rate for rupture at 30 days fell from 43·0 to 30·3 per cent, the total case fatality fell only slightly from 1985–1989 to 1990–1994.

Discussion

For two decades, studies in Western Australia[1,21], Europe[2,3,5–7] and North America[4,22–25] have reported increasing rates of incidence, surgical treatment and mortality from AAA. The results of this study suggest a fall in these rates since 1992 (*Figs 1* and *2*), a finding that has not been reported previously. In men, there have been falls in the age-standardized rates for non-ruptured and ruptured AAA procedures (*Fig. 2a*), and a fall in mortality from ruptured AAA (*Fig. 3*). A similar trend in elective procedures was seen in women, although the procedure rate for rupture has risen (*Fig. 2b*). These trends were more obvious for men owing to their greater numbers.

The annual rates for ruptured AAA were variable and the recent downward trend may be due merely to temporary variation. It could be speculated that the rate of elective surgery is now high enough to reduce the number of AAAs at risk of rupture, and that this has led to a stabilization or fall in the rates of operation for rupture (*Fig. 2*). The decline in the operation rate has in turn resulted in a fall in age-standardized mortality from rupture (*Fig. 3*).

Although the crude operative mortality rate for emergency aneurysm repair fell by 12·7 per cent at 30 days between 1985–1989 and 1990–1994 (*Table 1*), the 'total case fatality rate' for all ruptures, including patients who died without being admitted to hospital, did not change significantly for the same interval, indicating that the overall salvage rate was unchanged (*Table 2*). These data emphasize the lethal nature of ruptured AAA with over 40 per cent of deaths occurring without hospital admission; these cases are often overlooked in reports using institutional rather than community-based data.

The reason for the possible recent fall in the rate of elective surgery is unclear at present. The authors are unable to identify changes in the management of aneurysms in Western Australia that account for the decline in elective surgery. There is no reason for the diagnostic rate or the referral rate of AAA to have fallen in recent years given the increased use of ultrasonography and improved awareness of AAA. The decline in elective procedures cannot be accounted for by a reduction in the proportion of patients being offered surgery, as the criteria for elective surgery have not changed during the study interval. Nor can the fall be attributed to the introduction of endoluminal stent grafting in Western Australia since 1993 (*Fig. 1*), because its use has generally been restricted to patients at higher risk[26,27]. One possible interpretation is that the previous increase in operation rates (up to 1992) has allowed surgeons to 'clear the backlog' and establish a lower stable rate for elective procedures.

The possibility that trends in the procedure and mortality rate are unrelated to medical intervention but are due to changes in the true incidence rate of AAA needs also to be considered. The incidences of ischaemic heart disease and cerebrovascular disease have fallen in the past few decades[1,28]. These trends have generally been attributed to changes in cardiovascular risk factors[29]. As the dominant risk factors for AAA are the same as those for atherosclerosis[30], the trends in AAA may merely have lagged behind.

There have also been significant changes in the health of the Australian community which may explain why the declining trend for AAA has been observed in Western Australia before Europe or North America. The success of the antismoking movement in Australia[31,32] has contributed to a decline in the mortality rate in men from lung cancer since the mid-1980s[33,34]. This is the first time that this has been reported since the turn of the century[35]. As smoking is an important risk factor for both lung cancer[35] and AAA[36], a similar trend for AAA may be the result as the cohort of lifetime non-smoking men moves into the seventh and eighth decades.

Acknowledgements

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Arteriovenous fistula using transposed basilic vein

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Background Patients who need long-term haemodialysis often require multiple operations to maintain their vascular access. The options for secondary or tertiary access procedures may become increasingly limited. Prosthetic conduits are commonly used in difficult cases but are associated with a high incidence of complications.

Methods The brachial artery–transposed basilic vein arteriovenous fistula has been used in preference to a prosthetic graft on 31 occasions.

Results There were no technical failures and 28 of these fistulas matured. No major infective complications occurred.

Conclusion This procedure should be considered before resorting to a prosthetic graft for vascular access.

The provision of long-term vascular access for chronic haemodialysis remains a surgical challenge. The radiocephalic fistula of Brescia and colleagues[1], fashioned in the non-dominant arm, remains the undisputed first choice access procedure. However, a number of patients lack suitable vein in the forearm and thus alternatives are required. In addition, the extended life expectancy which has accompanied improvements in haemodialysis techniques can necessitate secondary and occasionally tertiary access procedures. If the cephalic vein is unsuitable in the upper arm, the choice of conduit is between prosthetic graft or transposed basilic vein. The deep subfascial position of the basilic vein protects it from cannulation or repeated venepuncture and it is generally of large calibre. Brachiobasilic arteriovenous fistula using transposed basilic vein was first described in 1976[2] but its place in the provision of long-term vascular access remains uncertain. Originally described as a tertiary procedure it has also been advocated as the second choice after Brescia–Cimino fistula[3]. In this unit, brachiobasilic fistulas have been fashioned in preference to use of a prosthetic graft in the small number of patients in whom the cephalic vein was not available in either arm. This report outlines the authors' experience with this procedure.

Patients and methods

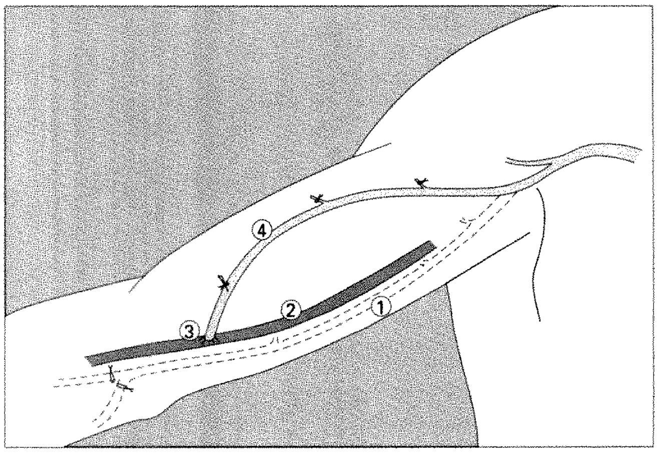
Brachiobasilic fistulas were fashioned using a technique similar to that described by Dagher *et al.*[2]. At each operation a single preoperative dose of co-amoxiclav 1·2 g was given intravenously. A transverse incision was made in the antecubital fossa and the deep fascia opened medially to expose the basilic vein. The incision was then extended up the medial side of the arm ('hockey stick' incision) and the whole length of the basilic vein was mobilized from beneath the fascia, taking care to preserve the medial cutaneous nerve of the forearm. Communicating tributaries were divided between 3/0 polyglactin ligatures and the vein was divided distally in the antecubital fossa. It was then transposed to a subcutaneous tunnel on the anterior surface of the arm and anastomosed end to side to the brachial artery in the antecubital fossa using 7/0 polypropylene (*Fig. 1*). A suction drain was sited beneath the deep fascia in the original site of the basilic vein, and an epidural catheter was placed in the axillary sheath to facilitate postoperative regional analgesia[4]. The wound was then closed in two layers. The drain was removed when there was less than 30 ml drainage fluid in the previous 24 h. The fistula was allowed at least 6 weeks to develop before venepuncture for dialysis.

Data concerning development of the fistula and use for dialysis were collected by retrospective review of the case notes and by prospective enquiry of individual patients and dialysis units.

Results

Thirty-one brachiobasilic fistulas were fashioned in 30 patients, ten men and 20 women of median age 60 (range 32–77) years. The left arm was used in 18 patients and the right arm in 13. In 13 patients this was the first vascular access procedure; suitable forearm or upper arm cephalic vein was absent. Seventeen patients had previously had arteriovenous fistulas: the median number of previous access procedures in this group was 2 (range 1–9).

There were no technical complications: all 31 fistulas were patent at 6 weeks. There was no perioperative death.



① = Basilic vein beneath deep fascia
② = Brachial artery
③ = Arteriovenous anastomosis-end to side
④ = Basilic vein transposed to subcutaneous position

Fig. 1 Use of the basilic vein for arteriovenous fistula

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There were four postoperative complications involving the wound: two postoperative haematomas, one wound infection which responded to oral antibiotics and a lymph leak from the antecubital fossa which settled spontaneously. No fistula subsequently became infected.

Of 31 procedures, 28 fistulas matured sufficiently to allow needling for dialysis. One patient died from cardiovascular causes before maturation. One fistula failed to develop as a consequence of a stenosis in the basilic vein and a third fistula was found to have thrombosed after the initial puncture. However, only 23 fistulas have been used for dialysis; two patients recovered renal function and one patient elected to return to peritoneal dialysis. Two fistulas were ligated before they were used because of steal phenomena which failed to settle. High-output heart failure, previously reported as a complication of arteriovenous fistula involving the brachial artery, was not seen.

Of 23 fistulas which have been used regularly for dialysis, 18 are still being used after a median follow up of 8 (range 2–18) months. Two patients have had a renal transplant and the fistulas are no longer in use but remain patent. In addition, one fistula remains patent but is no longer in use because of a bleeding diathesis. One fistula has failed because of multiple stenoses consequent upon repeated needling and a second has been ligated because of arm swelling secondary to a subclavian vein occlusion which occurred 14 months after the fistula was fashioned.

Discussion

Patients who require long-term haemodialysis need long-term vascular access. Multiple operations may be required to maintain access as time passes. The radiocephalic forearm fistula of Brescia and Cimino is well established as the operation of first choice and has a good long-term patency rate, once established. Unfortunately, adequate vein in the forearm is often not available[5]. In this situation a fistula fashioned by end-to-side anastomosis of the upper arm cephalic vein to the brachial artery in the antecubital fossa has been the procedure of second choice. If all the superficial veins are unavailable, formation of an arteriovenous fistula necessitates the use of either transposed autologous vein or a prosthetic graft. The patency rates of polytetrafluoroethylene grafts in this situation are 65–70 per cent at 1 year[3,6] and 50–65 per cent at 3 years[5,7]. However, these encouraging patency rates are only achieved at the expense of a considerable number of complications. A significant rate of spontaneous thrombosis is seen in prosthetic grafts such that an average of one thrombectomy operation per graft per year is required to maintain patency[8]. Furthermore, graft infection is dauntingly common, with rates of up to 15 per cent[9], and usually necessitates removal of the graft. This can be serious if the options for revision or establishment of temporary access are limited. Autologous vein has less tendency to spontaneous thrombosis and infection is usually treatable without loss of the fistula. Vein transposition does not preclude subsequent use of a prosthetic conduit at the same site[10] whereas it is unlikely that the converse would be successful. The brachiobasilic fistula gives patency rates approaching 60 per cent at 3 years in the hands of the originators of the technique[11,12] and these results have been matched in a large European series[13]. Published experience with this procedure in the UK is limited[14]. The present series is not sufficiently large to allow meaningful life-table analysis but the results are sufficiently encouraging to suggest that the brachial artery–transposed basilic vein arteriovenous fistula can form a valuable part of the vascular access surgeon's armamentarium.

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Multimodality treatment in the control of deep musculoaponeurotic fibromatosis

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Background Deep musculoaponeurotic fibromatoses are rare soft tissue neoplasms with a propensity for local recurrence.

Methods A retrospective analysis was carried out of the factors contributing to local disease control in 75 patients treated between 1963 and 1993.

Results Multivariate analysis identified the type of surgical excision ($P < 0{\cdot}001$) and involvement of pathological resection margins ($P < 0{\cdot}02$) as significant factors contributing to local recurrence. After a median follow up of 47 months (range 24 months to 29 years) 31 (49 per cent) of the 63 patients who had an 'adequate' surgical resection developed local recurrence. The median time before development of local recurrence was 83·4 (range 8–129) months in patients with clear pathological resection margins. This was significantly shortened to 13·1 (range 2–35) months in those with positive margins ($P < 0{\cdot}001$).

Conclusion Adequate surgical extirpation is the most important determinant in local disease control. Treatment of local recurrence ranged from observation during periods of disease stabilization to multimodality treatment for aggressive disease.

Musculoaponeurotic fibromatoses or desmoid tumours are rare soft tissue neoplasms constituting 0·03 per cent of all tumours with an incidence of 3·7 new cases per 10^6 of the population[1].

The growth pattern of these lesions mimics that of low-grade malignant tumours with a propensity for local tissue invasion. They present diagnostic as well as treatment difficulties. Although these tumours are 'benign' by virtue of being non-metastasizing, they are potentially hazardous because of their ability to grow to a large size, to interfere with function, to ulcerate and to involve vital structures. This study evaluates the factors contributing to local tumour control.

Patients and methods

A retrospective study was carried out on patients presenting with deep fibromatoses between 1963 and 1993. Ninety-five patients were assessed initially. Patients with superficial fibromatosis and those with Gardeners syndrome were excluded from this analysis.

Definitive histology was obtained in all cases, either by pathological review of outside material or, when inadequate, by further biopsy. Fibromatosis is an infiltrating proliferation of uniform bland fibroblasts and myofibroblasts (which also shows some of the features of smooth muscle cells) evenly dispersed within a collagenous stroma containing characteristic blood vessels and frequent mast cells[2]. The histological sections were all reviewed by a single pathologist.

Five patients with less than 2 years' follow-up and three with a revised diagnosis were excluded from subsequent analysis. Twelve further patients from abroad were lost to follow-up shortly after diagnosis leaving a total of 75 evaluable patients with a substantiated diagnosis of deep musculoaponeurotic fibromatosis.

Patient treatment was based on the principles of management developed from an extensive experience treating adult soft tissue sarcomas at this centre. The treatment plan was where possible on anatomical grounds to achieve wide surgical resection. In patients where only a marginal resection was possible consideration was given to adjuvant radiotherapy.

Twenty-seven patients presented with a previously untreated mass, 37 patients were referred for management of a local recurrence and an additional 11 patients were referred with inoperable disease. Preoperative assessment in the later part of the series involved computed tomography (CT). Patients were followed up at 3-month intervals for the first 2 years, 6 monthly for the next 2 years and yearly thereafter.

The initial treatment was surgical in 64 (85 per cent) of the patients. The principal aim of surgery was to obtain wide local clearance of tumour in order to achieve local control, whilst striving to preserve function. The surgical clearance achieved by initial surgery was recorded according to the Enneking classification[3], and was radical in seven patients, wide in 23 patients, marginal in 32 and intracapsular in 13 patients. To fulfil the surgical aim 32 of the 37 patients initially treated elsewhere had further surgery when referred, 28 having previously had a marginal excision and four with tumours for which only open diagnostic biopsy had been performed.

The majority of patients ($n = 52$, 69 per cent) did not receive radiotherapy. Thirteen of 37 patients had radiotherapy after surgical resection of locally recurrent disease. Five of 11 patients who presented with inoperable disease had primary radiotherapy and five patients with no evaluable disease received adjuvant radiotherapy after surgical resection.

Chemotherapy was only given to four patients (5 per cent), one with inoperable disease of the head and neck and to three patients for control of resistant local recurrence that had progressed despite other treatment.

Patients with inoperable or recurrent disease were treated initially by observation and/or hormonal manipulation with tamoxifen or its chlorinated analogue toremifen. Patients with progressive symptomatic disease had a combination of palliative chemotherapy, radiotherapy and debulking surgery.

The age and sex distribution of the patients is shown in *Fig. 1*. Disease-free survival was measured from the time of definitive diagnosis for the 63 patients having surgery with curative intent using the Kaplan–Meier product limit method and compared by the log rank test[4] (*Figs 2* and *3*).

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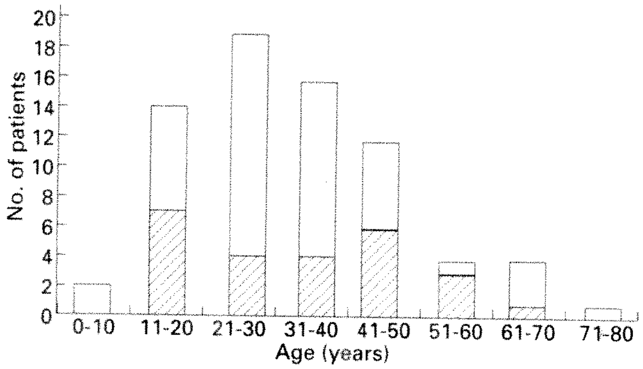
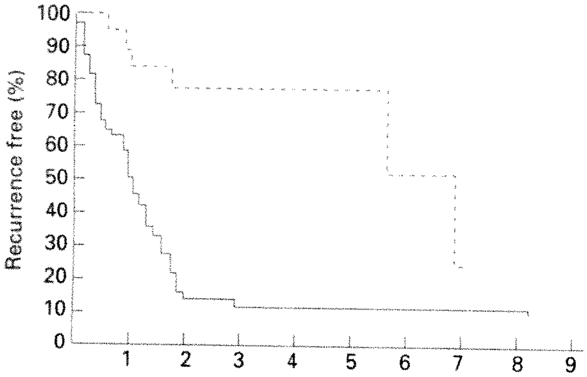
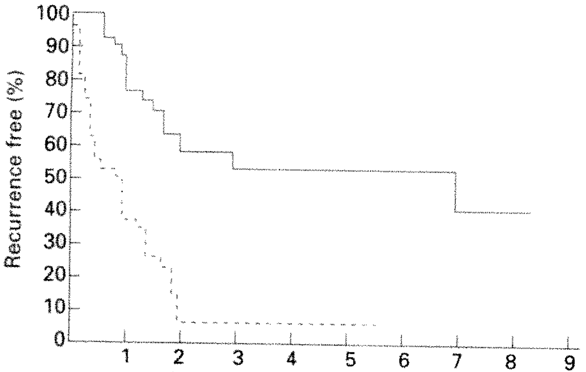


Fig. 1 Age and sex distribution of patients with desmoid tumours. □, female; ▨, male



Nos at risk									
Clear	19	17	15	15	15	15	10	5	
Involved	44	22	7	5	5	5	5	5	5

Fig. 2 Time to first recurrence in patients with clear (- - - -) or involved (——) pathological margins. $P < 0{\cdot}001$ (log rank test)



Nos at risk									
Radical and wide	31	24	18	16	16	16	16	12	12
Marginal and simple	32	12	2	2	2	2			

Fig. 3 Time to first recurrence in patients who had marginal and simple excision (- - - -) or radical and wide excision (——). $P < 0{\cdot}0001$ (log rank test)

Table 1 Fibromatosis tumour distribution by anatomical site

Anatomical location	No. of patients
Head and neck	10 (13)
Shoulder region	13 (17)
Upper limb	3 (4)
Abdominal and chest wall	19 (25)
Intra-abdominal	6 (8)
Pelvis	9 (12)
Lower limb	15 (20)
Total	75 (100)

Results

The median age of the patients was 30 (interquartile range (i.q.r.) 21–41) years, there were 50 female and 25 male patients. The commonest presenting feature was a slow growing mass ($n = 63$; 84 per cent) with a median diameter of 6·5 (i.q.r. 4–10) cm. Only one patient had multifocal disease at presentation. The median follow-up for survivors was 47 months (range 24 months to 29 years). *Table 1* shows the anatomical distribution of these tumours.

Local recurrence developed in 14 of the 30 patients treated by wide or radical surgical resection. However, 30 of the 33 patients with initial marginal or intracapsular resections had residual disease or early recurrence at the time of referral. Seventeen of these 33 patients were subsequently salvaged at this centre by additional surgical resection alone. In total 31 (49 per cent) of the 63 operable patients developed local recurrence after definitive resection and initial surgical control of disease.

Multiple recurrences developed in 24 (32 per cent) of the 75 patients observed over the follow-up period. Eight patients had two recurrences, ten had three and six had four or more. Two of these patients had a total of nine recurrences and eventually died from progressive disease within the abdomen and neck regions despite multimodality treatment.

The median time to development of a clinical recurrence requiring a change in treatment in patients with clear pathological margins was 83·4 (range 8–129) months. In patients who had involved pathological margins the median time to recurrence was significantly reduced ($P < 0{\cdot}001$) to 13·1 months although there was a wide range from 2 to 35 months. Of the 26 patients who subsequently were treated by further surgery achieving clear pathological margins 16 developed a second recurrence after a mean of 21·2 months, not significantly shorter than that achieved by adequate primary surgery.

Univariate and multivariate analysis of the clinical and pathological treatment variables on the rate of local recurrence was carried out as shown in *Table 2*. In the univariate analysis, of the pathological features analysed, the type of surgical excision and the adequacy of surgical margins significantly influenced the rate of local recurrence. A marginal surgical resection, clinically involved surgical margins and involved pathological resection margins were each associated with a significantly increased risk of local recurrence.

In a multivariate analysis all co-variates listed in *Table 2* were entered into a Cox proportional hazards model. Of the co-variates analysed the type of surgical resection and the involvement of pathological margins were both found to be independent risk factors. Wide or radical surgical resections ($P < 0{\cdot}001$) and clear pathological resection

Table 2 Univariate and multivariate analysis of factors contributing to local recurrence

	Hazard ratio	P
Significant factors on univariate analysis		
Operative resection		
Radical and wide	1·00	0·0001
Marginal and simple	4·74 (2·41–9·29)	
Surgical macroscopic clearance		
Achieved	1·00	0·001
Not achieved	3·16 (1·68–5·94)	
Pathological resection margins		
Clear	1·00	0·0001
Involved	4·69 (1·96–11·10)	
Significant factors on multivariate analysis		
Operative resection		
Radical and wide	1·00	0·001
Marginal and simple	3·28 (1·58–6·85)	
Pathological resection margins		
Clear	1·00	0·02
Involved	2·82 (1·10–7·14)	

Values in parentheses are 95 per cent confidence intervals. Co-variates in the multivariate analysis were age (less than 20, 20–30, more than 30 years), site of tumour, size of tumour (less than 5 cm, more than 5 cm), primary treatment, surgical clearance, pathological involvement of resection margins, type of surgical resection, number of recurrences, radiotherapy

margins ($P < 0·02$) were associated with a decreased risk of local recurrence.

Of the 63 patients who had surgery as the primary treatment modality 50 are disease free, 11 are alive with recurrence and two have died from disease. Of the 11 with recurrence four have progressive disease despite multimodality treatment, and seven have disease stabilization and are currently being treated by hormone manipulation or observation only.

A total of 14 patients had a period of hormone manipulation or observation only for recurrent or inoperable disease. Disease stabilization lasting over 1 year was found in four patients and over 6 months in a further five patients. Complete resolution was observed in one patient. Progressive symptomatic disease requiring a change of treatment occurred in the other four patients observed initially.

Discussion

The local invasion of fibromatosis[5,6] and the frequent recurrences have led some institutions to consider them as malignant soft tissue neoplasms[7–10]. Despite the benign pathology in terms of management the authors consider them equivalent to low-grade soft tissue sarcomas. Although fibromatoses frequently recur locally they have no metastatic potential. It is important for them to be distinguished from the histologically similar low-grade fibromyxoid sarcoma[11].

The natural history of untreated fibromatosis is one of slow progressive invasion of contiguous structures. Although the majority of patients who had an inadequate resection in this series went on to develop a local recurrence a long latent period of disease stabilization in some patients with evaluable disease was observed. This has led to an initial observation policy for local recurrence in areas where further adequate re-excision would result in functional impairment. Only one patient with a complete spontaneous resolution of tumour was observed. This rare phenomenon cannot be relied upon.

This series records several interesting features of the disease. These include complete spontaneous resolution, an occasional dramatic response to hormone manipulation, long quiescent periods after periods of rapid growth and the observation that not all tumours excised with positive resection margins progressed into a clinical recurrence.

The preponderance of deep fibromatosis in women of child-bearing age together with the rare spontaneous tumour regression seen during menarche and at the menopause raises the possibility of manipulative endocrine therapies. Although the precise relationship between these fibromatoses, the endogenous hormonal environment and exogenously administered endocrine therapies is far from clear, there is an established therapeutic relationship. Endocrine manipulations have resulted in some dramatic responses but there have been frequent failures[12].

Some authors have commented on the strong association with trauma[13]. Antecedent trauma or surgery was recorded in only one patient (1·3 per cent) in this series. It should be noted that minor trauma is common and, although not causative, may bring a patient's attention to a previously unnoticed mass.

Adequate surgical extirpation is clearly the most important determinant of local disease control as suggested by previous studies[7,14–16]. The more conservative approach advocated by some institutions[1,16–18] cannot be recommended. There appeared to be a local disease control advantage only if there was macroscopic clearance of tumour. The present findings suggest that 'salvage' wide excision following an initial incomplete excision conferred a similar advantage to initial wide excision, with no detriment to ultimate disease control.

The adjuvant effect of radiotherapy is less easy to verify. The initial results of Musgrove and McDonald[19] were interpreted as showing no role for radiotherapy. More recent series using megavoltage equipment have shown a more consistent response[20–26]. Relapse was associated with lower total dose (less than 50 Gy), small field size and orthovoltage techniques. Adjuvant radiotherapy was not given routinely in this series, to reduce the potential long-term sequelae of such treatment. Radiotherapy was confined to patients with inadequate tumour clearance where a wider clearance was not feasible on anatomical or functional grounds, or where recurrence had occurred with a short disease-free interval.

Unfortunately there are groups of patients in whom neither wide surgical resection nor radical radiotherapy may be feasible because the anatomical location, extent of disease and encroachment of vital organs render these treatment modalities inappropriate.

The characteristic infiltrative nature of desmoid tumours together with their frequent deep location renders their precise clinical anatomical localization difficult. CT and nuclear magnetic resonance imaging both contribute to the assessment of tumour extension and should be considered in all treatment planning which relies on identification of tumour margins. The deep fibromatoses have characteristic appearances on CT demonstrating homogeneity both before and after administration of intravenous contrast.

In conclusion, wide excisional surgery whenever possible should be considered the treatment of choice.

The overall additional benefit of radiotherapy remains controversial and to avoid late sequelae in a relatively young group of patients the authors do not use this modality routinely. In some patients recurrent disease can plateau after a period of rapid growth and can remain stable with minimal symptoms for long periods of time. This observation has modified the criteria for treatment of recurrent disease and an initial period of observation may be permissible.

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Anovestibular fistula to Bartholin's gland

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Background Acquired fistulation from the anal canal to Bartholin's gland has not been reported before. This fistula has been identified in 11 women treated between 1991 and 1995.

Methods All discharge diagnoses during this period were searched. The clinical records of patients managed for this diagnosis were reviewed.

Results Eleven women aged 24–49 years were identified. Seven of 11 fistulas arose in association with inflammatory bowel disease (five Crohn's disease, two ulcerative colitis). Patients typically presented with the vulval passage of flatus and faeces or acute sepsis of Bartholin's gland. Time to diagnosis of the fistula ranged from 1 to 15 (median 8) months after the onset of symptoms. Anatomically, all fistulas were high trans-sphincteric or suprasphincteric. All eight fistulas for which repair was attempted (five in the presence of inflammatory bowel disease) remain healed at short-term follow-up. Proctocolectomy was undertaken in two patients with severe Crohn's colitis.

Conclusion Ano–Bartholin's fistulas, although rare in general surgical practice, present with troublesome symptoms and may be repaired successfully. Gynaecologists and surgeons should be aware of this clinical entity to avoid unnecessary delays in treatment.

Either through uncertainty or embarrassment, women may delay reporting the vulval passage of flatus or faeces. Clinical diagnosis of proctovaginal fistula of any configuration rests on the positive identification of a fistulous tract. Most such fistulas are quite easily confirmed by identification of the vaginal opening in the vicinity of the posterior fourchette. However, if the vaginal opening cannot readily be detected, the correct diagnosis may be further delayed. Thus, one reason for diagnostic difficulty is unusual fistula anatomy. To the authors' knowledge, no previous description of spontaneously acquired ano–Bartholin's fistula exists in the literature although it is suspected that anovestibular fistula to Bartholin's gland is more common than its limited bibliography suggests.

Patients and methods

The hospital records of 11 women aged 24–49 (median 34) years who had the diagnosis of ano–Bartholin's gland fistula made or referred to in the course of their management between 1991 and 1995 were reviewed. A further patient seen several years earlier was included because clinical photography of the case is particularly illustrative (*Fig. 1*).

Results

Seven fistulas were found in women with inflammatory bowel disease (IBD), two of whom had ulcerative colitis and five had Crohn's disease; two of the latter had no previous anal lesion. Four had no evidence of IBD; the aetiology of these fistulas was assumed to be idiopathic anal sepsis. In all cases, standard clinical and histopathological criteria for the differential diagnosis of IBD were used by staff at St Mark's Hospital. Symptom duration was 1–15 (median 8) months before diagnosis which was generally made under anaesthesia. All fistulas were classified anatomically as high trans-sphincteric or

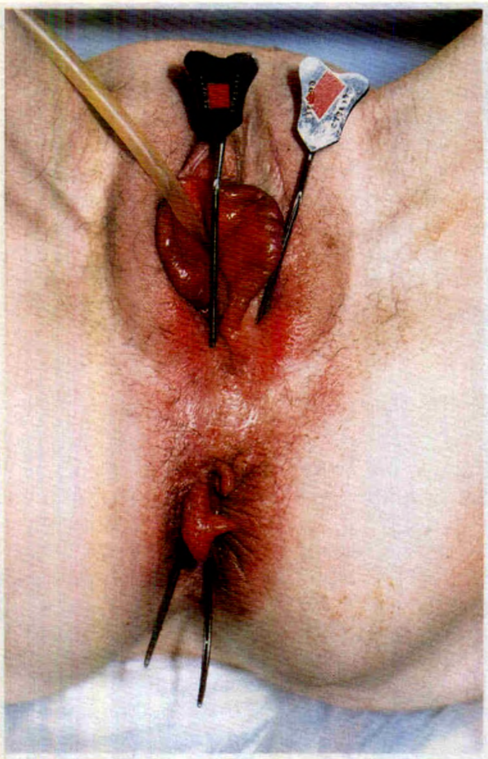

Fig. 1 Two fistula probes pass from the vulval openings of Bartholin's glands to a single internal opening in the anal canal in a patient with Crohn's disease. Of particular note is the absence of inflammation or granulation tissue in the region of the glandular orifice. This patient was managed by proctocolectomy because of her generally poor state of health from concomitant pulmonary disease

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Table 1 Clinical details of patients with anal fistula to Bartholin's gland from 1991 to 1995

Age (years)	Inflammatory bowel disease at diagnosis	Perineal symptoms	Symptom duration (months)	Diagnostic tool	Fistula anatomy	Treatment	Fistula healed
32	Crohn's disease	Severe perineal sepsis	2	EUA	Suprasphincteric	Ileostomy and fistula laid open; subsequent repair	Yes
25	Ulcerative colitis	Acute vulval abscess	1	EUA	Suprasphincteric	Advancement flap	Yes
34	Ulcerative colitis	Faeculent p.v. discharge	15	Anal ultrasonography	Suprasphincteric	Seton then advancement flap	Yes
24	None	Bartholin's 'cyst'	8	EUA	High trans-sphincteric	Advancement flap	Yes
40	None	Bartholin's abscess	11	EUA	High trans-sphincteric	Excision and sphincter repair	Yes
28	Crohn's disease (not anal)	Bartholin's cyst marsupialized, then p.v. discharge	12	EUA	High trans-sphincteric	Excision and sphincter repair	Yes
37	None	Faeculent p.v. discharge; three previous Bartholin's operations	12	EUA	Suprasphincteric	Advancement flap	Yes
49	Crohn's disease (colon)	Bartholin's cyst, then abscess and p.v. discharge	6	EUA	Suprasphincteric	Proctocolectomy	—
34	None	Bartholin's cyst drained, then faeculent discharge	6	EUA	High trans-sphincteric	'Permanent' loose seton	No
39	Crohn's disease (not anal)	Faeculent p.v. discharge	12	EUA	Suprasphincteric	Excision and sphincter repair	Yes, two operations
47	Crohn's disease (colon)	Severe perianal sepsis	1	EUA	Suprasphincteric	Proctocolectomy	—

EUA, examination under anaesthesia; p.v., per vaginum

suprasphincteric. Some fistulas found in association with Crohn's disease were complex or bilateral (*Fig. 1*).

Closure of the fistula was achieved in the majority of cases. One woman (without IBD) had complete symptom control after placement of a loose seton and has deferred further treatment to date. Other fistulas were closed either by advancement flap repair or by excision of the track and anterior sphincter repair. All eight fistulas in which repair was attempted (five in the presence of IBD) remain healed at short follow-up. Proctocolectomy was undertaken in two women with severe perianal Crohn's disease.

Discussion

Congenital anovestibular and anovulvar fistulas with a normal anus are very rare in clinical practice[1,2] and iatrogenic, acquired fistulas have been reported only twice in the literature[3,4]; diagnosis of the condition may be delayed for this reason alone. Further evaluation of the records in this institution identified approximately 60 women who received treatment for more usually configured anovaginal or rectovaginal fistulas (the distinction between these is difficult because of an overlap in terminology between the two). Ano–Bartholin's fistula, therefore, seems to be a relatively uncommon occurrence compared with the 'standard' fistula, although relative frequencies of these conditions are distorted by referral practices to the hospital, and the fact that many proctovaginal fistulas were identified after restorative proctocolectomy.

Bartholin's (greater vestibular) glands are derived from diverticula arising from the epithelial lining of the urogenital sinus once it has separated from the hindgut. Thus, a developmental anomaly which would readily account for a fistula arising between Bartholin's glands and the anal canal is unlikely[5]. It is more probable that the fistula described here is initiated by idiopathic anal sepsis tracking anteriorly rather than infection in Bartholin's gland spreading back to the anal canal. The particular importance of this clinical entity is that the 'external' opening of the fistula is not readily identifiable in its common site in the posterior fourchette; very often, unless it is associated with Bartholin's gland sepsis, its vulval orifice is normal in appearance or only slightly oedematous. The fistula can be identified only by palpation of subcutaneous induration leading from the anus to the region of the gland in the labium majora.

Two similar reports refer to rectovaginal fistulas secondary to excision of Bartholin's gland, suggesting that the rectal wall was breached at operation[3,4]. In one of these patients the fistula was not related to the anal sphincter and was probably of different aetiology. In the present similar cases, Bartholinectomy had not been undertaken; damage to the anal canal would have been improbable during lesser surgery.

Many patients with Crohn's disease expect perineal symptoms and may not declare them, perhaps for fear of a defunctioning stoma; thus, fistulas occurring in association with IBD may be tolerated for longer than the idiopathic variety. Despite this, considerable periods elapsed between symptom onset and diagnosis, particularly in those with idiopathic fistulas. Although the most frequent source of perineal fistula in Crohn's disease is the anus, another possibility is that extragastrointestinal Crohn's disease may arise primarily in the vulva. This situation has been reported previously when vulval lesions containing Crohn's granulomata unconnected to the gastrointestinal tract were found in three patients[6].

It is concluded that when suggestive symptoms are reported without an evident anovaginal fistula, women should be investigated by examination under anaesthesia to exclude an ano–Bartholin's gland fistula. Furthermore, during surgery for acute Bartholin's gland sepsis, examination of the anus should be undertaken to exclude primary anal pathology. Surgical treatment of such fistulas offers an excellent chance of healing.

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Outcome following laparoscopic resection for colorectal cancer

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Background A prospective comparison of laparoscopic or laparoscopically assisted colorectal resection *versus* open resection has been undertaken to evaluate early benefits and cost implications.

Methods Consecutive patients with colorectal cancer underwent either elective laparoscopic ($n = 25$) or open ($n = 29$) resection.

Results Mean hospital stay was significantly shorter in the laparoscopic group: 10·7 *versus* 17·8 days. Mean morphine requirements were less in patients who had laparoscopic resection and their recovery, as measured by the dynamometer hand grip and the SF-36 symptom score, was more rapid. Adequate tumour clearance was achieved in the laparoscopic group. In both groups, the number of lymph nodes harvested was similar. Port-site or wound recurrence has not been observed at a median follow-up of 28 months.

Conclusion When laparoscopic colorectal resection is possible, there are significant early benefits for patients.

The application of laparoscopic techniques to the resection of colorectal cancer has not gained universal acceptance for three main reasons: the learning curve is longer than that for laparoscopic cholecystectomy; there have been reports of cancer implantation in laparoscopic port sites[1–5]; the presence of an anastomosis or stoma prevents rapid discharge from hospital. Provided minimal access techniques do not compromise cancer cure it is appropriate to question whether laparoscopic colorectal resection improves recovery compared with conventional surgery. Patients undergoing resection for colorectal cancer were studied prospectively and results following laparoscopic resection were compared with those following open operation.

Patients and methods

From February 1994 for 24 months, consecutive patients undergoing elective resection for colorectal cancer had either laparoscopic or laparoscopically assisted resection or open resection. Indications for open resection were: patient preference, gross obesity, widely separate synchronous tumours, tumour fixation and/or a palpable mass (7 cm or more). Patients who presented as an emergency or who required urgent surgery, within 1–2 days of admission, were excluded.

All operations were performed by one surgical team under general anaesthesia and standard antibiotic prophylaxis. The techniques of laparoscopic and laparoscopically assisted resection have been described elsewhere[6]. Mobilization of the bowel and ligation of the vascular pedicle was carried out intracorporeally; individual clips or ligatures were used for the vessels, not stapling devices. Bowel anastomosis was performed either by hand, through a small incision, or stapled as in anterior resection. All wounds, including laparoscopic port sites, were lavaged with a 1 in 10 solution of povidone–iodine and the rectum was washed with the same solution before construction of the anastomosis. Patients with mid or low rectal cancer underwent total mesorectal excision[7,8].

Pain relief after operation was by intravenous morphine in the form of patient-controlled analgesia. Pain scores were measured using a linear analogue scale at 6 h, and 1, 2 and 3 days after operation. Morphine requirements were calculated for the same intervals. The dynamometer, which measures grip strength, was used to assess protein loss[9]. Measurement of weight, mid upper arm circumference, serum albumin concentration and dynamometer grip strength were made before operation, and at 1 and 6 weeks after surgery. The SF-36, a standard health evaluation questionnaire[10], was completed by the patient before operation, and at 2 and 4 months after operation. Data were also collected to analyse duration of operation and hospital stay, blood loss and transfusion requirement, readmission within 30 days of surgery, 30-day mortality rate, number of lymph nodes resected and the cost of each intervention (*Table 1*). Histological staging was based on Dukes classification[11].

Statistical analysis

Differences between groups were analysed using the t test and χ^2 test as appropriate. Allowance for potential confounding factors was made using analysis of covariance and linear regression. Where necessary logarithmic transformations were performed to bring skewed distributions nearer to normal and to ensure homoscedasticity.

Results

Laparoscopic resection was attempted in 25 patients, but in three conversion to open surgery was necessary. For purposes of analysis these three patients were included in the laparoscopic resection group as the intention had been to treat them laparoscopically. All other patients in the laparoscopic group underwent laparoscopically assisted resection, except two in whom abdominoperineal excision of the rectum (APR) was performed wholly laparoscopically. *Table 2* lists the operative procedures undertaken and *Table 3* the results following surgery.

Table 1 Cost of operation (£)

Cost of operation is calculated as the sum of:
Stay in Yeovil Hospital (days) × 165
Time in theatre (h) × 164
Stay in convalescent hospital (days) × 80
Cost of disposable equipment
Blood transfused (units) × 32
Cost of extra hospital stay if readmitted within 30 days
Cost of reoperation if necessary

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Table 2 Site of colorectal carcinoma and operative procedure

	Open resection	Laparoscopic resection
Site		
Right colon	9	3
Transverse colon	3	0
Left colon	3	1
Sigmoid colon	4	5
Rectum	10	16
Total	29	25
Procedure		
Right hemicolectomy	9	3
Transverse colectomy	3	0
Left hemicolectomy	3	1
Sigmoid colectomy	3	5
Anterior resection	7	6
Abdominoperineal excision of the rectum	2	9
Hartmann's operation	1	1
Total colectomy	1	0
Total	29	25

Table 3 Results following elective resection of colorectal cancer

	Open resection	Laparoscopic resection
No. of patients	29	25
Median follow-up (months)	26	30
Median age (years)	70	69
Dukes grade		
A	4	8
B	13	9
C	12	8
No. of lymph nodes in specimen*	7·7(4·2)	7·0(2·3)
ASA grade		
I	12	6
II	12	16
III	5	3
Duration of operation (min)*	123(41)	179(41)‡
Blood loss (ml)*	670(590)	474(390)
Blood transfusion (units)*	1·4(1·5)	1·1(2·0)
Mean duration of first admission at this hospital (days)	12·7	9·7‡
Mean stay at convalescent hospital (days)	5·1	1·0‡
Total hospital stay (days)*	17·8(9·5)	10·7(4·7)†
Cost of disposable equipment (£)*	140(200)	400(220)‡
Total cost of treatment (£)*	3300(1700)	2900(1500)
Readmission	4	3
Death within 30 days	2	1
Locoregional recurrence (palliative surgery)	1	1
Port-site or wound recurrence	0	0
Subsequent death from metastatic disease	8	4
Stoma formation	10	11
Dynamometer grip strength (percentage of preoperative value)		
1 week after operation	83	96¶
6 weeks after operation	92	104§

*Values are mean(s.d.). ASA, American Society of Anesthesiologists. †$P = 0{\cdot}001$, ‡$P < 0{\cdot}05$, §$P = 0{\cdot}06$, ¶$P = 0{\cdot}09$ *versus* open resection (*t* test)

The median age, tumour stage and American Society of Anesthesiologists (ASA) status were similar for patients in both groups (*Table 3*). Patients undergoing open anterior resection had tumours situated closer to the anal verge than those undergoing laparoscopic anterior resection (median 7 *versus* 13 cm). The anastomoses were situated at a similar median distance from the anal verge (3 cm). Patients who had open resection had a higher rate of stoma formation: five of seven *versus* two of six. The preponderance of APRs in the laparoscopic group occurred because an attempt was made to treat all low rectal tumours laparoscopically. The median distance of tumours from the anal verge in patients who had APR was 2 cm; all but one were within 3 cm. In two patients open APR was performed, one because of patient preference and the other for tumour fixation.

There were no intraoperative complications in patients undergoing laparoscopic resection such as haemorrhage, bowel perforation or ureteric injury. Three deaths occurred. One patient who underwent open anterior resection and left nephrectomy for renal adenocarcinoma died in renal failure at 14 days. Post-mortem examination revealed a second renal cell tumour. A second patient underwent open sigmoid colectomy, required a Hartmann procedure after 6 days for anastomotic leakage and died at 27 days from adult respiratory distress syndrome. One patient underwent a laparoscopically assisted anterior resection without a stoma for a proximal rectal tumour, had an anastomotic leak at 7 days and died at 10 days from fulminating sepsis despite conversion to a Hartmann procedure.

Hospital stay was significantly shorter in patients treated by laparoscopic resection (*Table 3*). Although laparoscopic resection increased operating times and the cost of disposable equipment, the total cost was less than for open resection (*P* not significant). Morphine requirements following laparoscopic resection were significantly lower than those after open resection (*Fig. 1*), but differences in pain scores did not reach significance. Differences in albumin concentration, weight, mid upper arm circumference and dynamometer grip strength between the two groups were not significantly different compared with preoperative values. Despite this, the

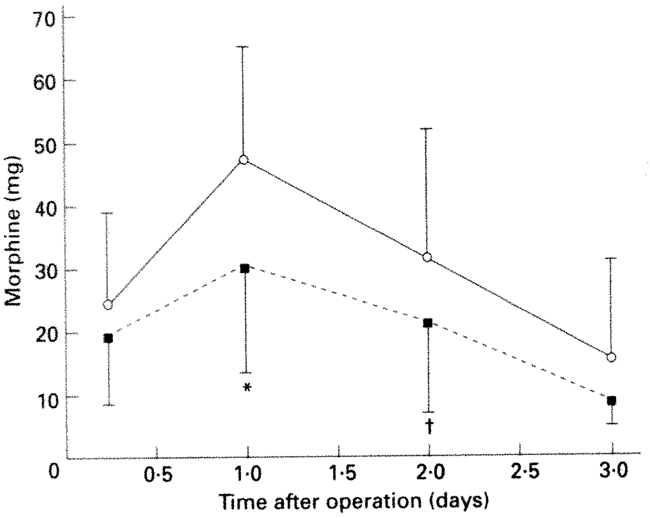

Fig. 1 Mean(s.d.) postoperative morphine requirement following laparoscopic (■) and open (○) colorectal resection. *$P = 0{\cdot}002$, †$P = 0{\cdot}06$ *versus* open resection (*t* test)

reduction in grip strength observed following open operation persisted for 6 weeks, whereas there was no reduction in this parameter at 6 weeks after laparoscopic resection (*Table 3*).

Analysis of results using the SF-36 questionnaire revealed that in six of the eight areas of questioning there was less impairment in health following laparoscopic resection (when compared with preoperative values) than open operation. This trend persisted at both 2 and 4 months but the difference was significant only in the 'general health' questions and then only at 2 months after operation. In two of the eight dimensions of the SF-36 the patients who had open resection had less impairment than those who had a laparoscopic procedure.

No port-site metastasis or unexpected locoregional recurrence has been detected after a laparoscopic procedure.

To allow for possible confounding factors, differences between groups were analysed while controlling for ASA grade, Dukes stage and age. Although some of these factors were significantly associated with the measured outcomes (e.g. age significantly affected length of stay), their inclusion in regression models did not alter the associations between operation type and outcomes described above for the simple analyses.

Discussion

This study has demonstrated a significantly shorter hospital stay in the patients selected for laparoscopic resection of colorectal cancer, by comparison with open resection. Dynamometer measurements and assessments using the SF-36 questionnaire supported the impression that recovery following laparoscopic resection was more rapid; some of the trends were even present 4 months after operation. Although sample sizes were small and the technique relatively new, these results justify further assessment. The selection criteria for each operative technique may have biased results and this needs to be addressed by a randomized controlled trial.

Short-term benefits of laparoscopic resection are irrelevant if they reduce the rate of tumour clearance, unless laparoscopic techniques compensate in some other way, for example by decreasing operative mortality. Most patients with port-site recurrence had advanced disease at the initial procedure or at the time the recurrence was diagnosed[12,13]. There have, however, been reports of local recurrence in patients with histologically early tumours[3,14]. The authors followed a policy of avoiding contact between laparoscopic instruments and the tumour, as well as meticulous lavage of all wounds with a cytocidal agent. The present results are similar to those of three of the largest reported studies, both with respect to local recurrence[15] and to lymph node numbers in the resection specimen[16,17]. This does not provide grounds for complacency, but neither should minimal access techniques be rejected unless there is sound proof of an oncological disadvantage.

These results of laparoscopic or laparoscopically assisted resection suggest that early benefits exist in patients selected for this type of surgery compared with conventional surgery. This trend was present for at least 4 months after operation, longer than described by others.

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Surgical treatment of severe duodenal polyposis in familial adenomatous polyposis

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Background Patients with familial adenomatous polyposis (FAP) are at risk for adenomas and cancers in the duodenum but the ideal management of duodenal polyposis remains uncertain.

Methods The outcome of surgical resection was analysed in 18 patients with FAP who had severe duodenal polyposis.

Results Duodenotomy and clearance of duodenal adenomas was performed seven times in six patients. There were two duodenal leaks and, after a mean follow-up of 53 (range 36–72) months, duodenal adenomas recurred in all patients and five had severe polyposis. Pancreatoduodenectomy was performed in seven patients with severe duodenal polyposis. Histology of the specimens revealed two unsuspected duodenal carcinomas at an early stage. After a mean follow-up of 42 months all patients were alive and well, and there was no case of jejunal polyposis. Pancreatoduodenectomy was attempted in five patients with duodenal cancer and only one survived more than 4 years.

Conclusion Surgical excision of duodenal adenomas should be discussed before carcinoma occurs. Surgical polypectomy fails to guarantee a polyp-free duodenum and carries a risk of postoperative complications whereas pancreatoduodenectomy eliminates the risk of duodenal cancer with an acceptable morbidity rate. Pancreatoduodenectomy could be offered to some patients with large or multiple villous duodenal adenomas repeatedly showing severe dysplasia.

Duodenal adenomas develop in most patients with familial adenomatous polyposis (FAP)[1,2] and there is growing evidence to suggest that the adenoma–carcinoma sequence occurs in the upper gastrointestinal tract. Pathological studies of duodenal cancer in FAP have revealed adenomatous tissue in 66 per cent of cases, and adenomas as a component of, or adjacent to, duodenal cancer in 84 per cent[3]. The incidence of periampullary cancer is estimated to be 200–300 times greater than that in the general population[4], and duodenal cancer accounts for the majority of cancer-related deaths after colectomy[5].

Although the natural history of duodenal adenoma is unknown and the reported incidence of duodenal cancer is low (37 (3 per cent) of 1255 registered patients[5]), classification of duodenal polyposis on a five-grade scale based on polyp number, size, histology and severity of dysplasia (*Table 1*) showed that patients with stage IV disease, accounting for about 10 per cent of patients with FAP, are at greatest risk of malignant change[6].

In these cases, endoscopic removal is often impractical because large and sessile polyps cannot be snared and perforation may occur whereas electrocoagulation may cause periampullary scarring and bile duct obstruction or pancreatitis. Therefore, preventive surgery may be indicated for patients who have rapid polyp growth and consistently severe dysplasia.

The aim of this study was to determine the outcome of patients with FAP with severe duodenal polyposis or duodenal cancer in whom a surgical approach had been used and to compare the results of polypectomy by duodenotomy and pancreatoduodenectomy.

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Table 1 Classification of the severity of duodenal polyposis (according to Spigelman *et al.*[1])

	No. of points		
	1	2	3
No. of polyps	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histology	Tubulous	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0, 0 points; stage I, 1–4 points; stage II, 5–6 points; stage III, 7–8 points; stage IV, 9–12 points

Patients and methods

Among the 260 patients treated for FAP in this hospital between 1983 and 1996, those who had undergone surgical treatment for duodenal adenoma or adenocarcinoma were identified from the medical records. Data obtained from retrospective review of these records included patient's age and sex, the type of colorectal resection, the findings at each upper gastrointestinal endoscopy session, the type of surgical resection of duodenal adenomas and the subsequent course of each patient regarding postoperative complications, recurrence of duodenal adenomas, bowel function and survival. The severity of duodenal polyposis was classified according to a system previously described by Spigelman *et al.*[1] in which variables that worsen the stage are increasing number, size, villous morphology and degree of dysplasia (*Table 1*). Severe duodenal polyposis was defined by stage IV polyposis with adenomas showing severe dysplasia at two repeated examinations.

Duodenotomy involved a Kocher manoeuvre, longitudinal incision of the second part of the duodenum, removal of larger polyps by a technique of submucosal infiltration and local incision with clearance of the remaining polyps in the duodenum by either excision or diathermy, transverse closure of the duodenal defect by a running one-layer suture of resorbable suture and drainage.

Pancreatoduodenectomy for severe duodenal polyposis was performed with pylorus preservation when the first part of the duodenum was free of polyps and the restorative procedure was a pancreaticogastric anastomosis. When duodenal cancer was suspected before operation or proven, a standard Whipple procedure was performed with pancreatojejunal anastomosis.

Results

Duodenotomy and clearance of duodenal polyps was performed seven times in six patients (five women) with stage IV duodenal polyposis, at a mean age of 40 (range 25–62) years. Some of the results in these patients have been published previously[7]. One patient had a previous coloproctectomy with ileostomy; in the other cases duodenotomy and restorative proctocolectomy with ileal J pouch–anal anastomosis (IPAA) was performed simultaneously. One patient had cholecystectomy on day 5 for acute cholecystitis. Two patients developed a duodenal fistula. One was treated medically and the other, which occurred after repeated duodenotomy, necessitated reoperation for closure and drainage. The histopathology of the resected specimens was similar to that of the preoperative evaluation in all cases. Duodenal adenomas recurred in all patients after 6–36 months. After a mean follow-up of 53 (range 36–72) months all but one patient had stage III or IV duodenal polyposis.

Pancreatoduodenectomy was attempted in 13 patients. Of the five patients with preoperative biopsy-proven duodenal carcinoma, resection was not possible in two cases because of peritoneal carcinomatosis or distal lymph node involvement, and death occurred within 12 months in both cases. The remaining three patients had a Whipple procedure with no perioperative complication. One patient with a tumour restricted to the muscle of the sphincter of Oddi without metastasis to lymph nodes was alive after 9 years of follow-up. The other two died at 17 months from peritoneal carcinomatosis and at 46 months from rectal cancer distal to an ileorectal anastomosis.

In eight patients (four women) with severe duodenal polyposis but without carcinoma on preoperative duodenal biopsy, pancreatoduodenectomy was attempted at a mean age of 54 (range 41–71) years for severe duodenal polyposis. All patients had had a previous colectomy: ileorectal anastomosis in four cases, abdominoperineal resection and ileostomy for stage II rectal cancer 7 years after ileorectal anastomosis in one case and IPAA in three. One patient had stage IV duodenal polyposis with severe dysplasia on a 2-cm indurated adenoma at the first endoscopy when he was 47 years old. The remaining seven patients were followed regularly with upper gastrointestinal endoscopy and progressed from stage 0–II to stage IV in a mean of 10 (range 5–16) years (*Table 2*). Symptoms related to duodenal polyps occurred in three cases: acute oedematous pancreatitis in one and upper gastrointestinal haemorrhage in two. Four patients had had previous endoscopic removal of duodenal adenomas and one had had removal of a large polyp by duodenotomy at the time of restorative proctocolectomy. Endoscopic treatment was not attempted in the other three patients because of the periampullary location of multiple and sessile adenomas. They received sulindac, which failed to stop the progression to stage IV disease in all cases. The presence of abdominal desmoid tumours precluded pancreatoduodenal resection in one patient who was still alive with stage IV polyposis 2 years later.

Pancreatoduodenectomy was performed in three other patients with limited desmoid tumours, but in one case with involvement of the root of the mesentery by the desmoid tumour the bile duct was transected in its lower portion to allow a tension free biliary–enteric anastomosis. In two of the three patients with previous IPAA the jejunal loop was placed behind the mesenteric root to avoid torsion of the mesenteric vessels and then anastomosed to the pylorus. The pylorus was preserved in all but one case in which the first portion of the duodenum was carpeted with polyps. There was no postoperative death.

Table 2 Follow-up data in eight patients with severe duodenal polyposis who had pancreatoduodenectomy

	First endoscopy		Endoscopy before operation							
Patient no.	Age (years)	Stage	Age (years)	Stage	Dysplasia	Operation	Histology of specimen	Postoperative course	Follow-up (months)	Jejunal biopsy
1	38	I	50	IV	Severe	ADT (no resection)	—	—	24	Stage IV, severe dysplasia
2	47	IV	47	IV	Severe	PP, PG	Severe dysplasia	—	108	95 months, no polyps
3	35	II	41	IV	Severe	PP, PG	Severe dysplasia	Pancreatic fistula	50	24 months, no polyps
4	55	0	60	IV	Severe	G, PG	Severe dysplasia	—	36	—
5	42	0	58	IV	Severe	PP, PG	Invasive carcinoma	—	48	20 months, no polyps
6	39	II	49	IV	Severe	PP, PG	Severe dysplasia	Upper gastrointestinal haemorrhage	24	12 months, no polyps
7	40	I	56	IV	Severe	PP, PG	Invasive carcinoma	—	9	6 months, no polyps
8	63	II	71	IV	Severe	PP, PG	Severe dysplasia	—	36	15 months, no polyps

ADT, abdominal desmoid tumour; PP, pylorus preservation; PG, pancreatogastric anastomosis; G, gastrectomy

The postoperative course was uneventful in five cases, one patient was reoperated on at day 9 for upper gastrointestinal haemorrhage originating from the duodenojejunal anastomosis, and another developed a low-output pancreatic fistula which was treated medically and healed spontaneously by day 17. Histopathological examination of the resected specimens revealed invasive carcinoma in two cases with no muscular invasion. After a mean follow-up of 42 (range 9–108) months all patients were alive and well, although one complained of duodenogastric reflux despite pylorus preservation. In the three patients with IPAA and the three with ileorectal anastomosis, bowel function was not affected by the procedure. The stomach and the jejunal loop were screened at least once in six patients, 6–95 months after the procedure. No gastric or jejunal polyps were found and random biopsies of the jejunal loop were normal.

Discussion

This study shows that duodenotomy and clearance of duodenal polyps was associated with postoperative complications and failed to guarantee a polyp-free duodenum in the long term. Pancreatoduodenectomy satisfactorily cured duodenal polyposis, allowed the complete removal of previously unsuspected duodenal carcinomas, was not associated with considerable morbidity and was feasible after restorative proctocolectomy. When duodenal carcinoma was present, resection was not always feasible and the outcome was poor.

In FAP, the management of multiple and large duodenal adenomas with severe dysplasia and not amenable to endoscopic removal remains controversial. The potential for such lesions to degenerate into carcinoma associated with the difficulties of diagnosis of carcinoma at an early stage despite regular surveillance[8] leads the authors to propose prophylactic surgical excision. Duodenotomy and clearance of duodenal polyps[7] or local excision of the ampulla[8] may considerably reduce the occurrence of malignancy but recurrence is the rule and, despite the potential morbidity of this type of surgery, patients should be regularly and indefinitely followed with upper gastrointestinal endoscopy.

Pancreatoduodenectomy is often seen as a major operation with mortality and morbidity rates unacceptable in the treatment of benign disease. On the other hand, when duodenal carcinoma has developed, the results of pancreatoduodenal resection are disappointing with a mean survival time of 42–57 months after resection of node-negative duodenal cancer and 6–16 months when lymph nodes are involved[9,10]. During the past decade, the postoperative mortality rate associated with pancreatoduodenal resection has decreased markedly. Several authors have reported numerous pancreatoduodenal resections without a death[11,12]. In a series of 108 pancreatoduodenectomies for benign disease, the mortality rate was less than 1 per cent and only two patients required reoperation for a complication, leading the authors to the conclusion that concerns about mortality and morbidity should not prevent an aggressive approach to surgical resection in patients with benign disease[13].

In the management of patients with FAP with severe duodenal polyposis, pylorus preservation and pancreatogastric anastomosis seems to present several advantages over the classical Whipple procedure. Pylorus preservation avoids gastric resection and procures a better functional outcome with fewer cases of dumping, diarrhoea and marginal ulceration[14]. The preserved pylorus reduces bile reflux into the stomach, which had been incriminated in gastric adenoma formation[15]. Pancreatogastric anastomosis is a simple reconstruction method[16] which offers several potential advantages including an easy tension-free anastomosis due to the natural disposition of the pancreas on the posterior wall of the stomach, a well vascularized anastomosis with the thick gastric wall with its excellent blood supply, a significant distance between biliary and pancreatic anastomoses obviating the deleterious effects of leakage of one on the other, and protection against anastomotic ulceration by alkaline pancreatic secretions[17,18]. Preservation of the entire stomach with an end-to-end duodenojejunal anastomosis and a choledochojejunostomy constructed 10 cm downstream[19] facilitates endoscopic screening of the remaining jejunum receiving bile outflow and helps to preserve bowel function after proctocolectomy in avoiding a blind-loop jejunostomy.

Although duodenal adenomas are seen in nearly all patients with FAP, the risk of developing duodenal carcinoma remains low. In the future, new treatments under evaluation such as photodynamic laser therapy and use of non-steroidal anti-inflammatory drugs may help to prevent adenoma formation or transformation[20]. However, for those in whom polyps are growing rapidly and when severe dysplasia is found at several histological examinations, surgical resection should be proposed before carcinoma develops. In these rare cases, pancreatoduodenal resection offers several advantages over polyp excision by duodenotomy and can be achieved with a low morbidity rate in experienced hands.

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Assessment of a scoring system for breast imaging

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Background Triple assessment is the standard method of assessing symptomatic breast lumps. There is an accepted format for reporting cytology but not for the reporting of mammograms or breast ultrasonographic images. This study describes a scoring system for reporting breast imaging methods.

Methods Patients with symptomatic breast lumps seen during 1 year were included. All patients underwent triple assessment. Imaging studies were reported using a grading system from 1 to 5. The results of triple assessment were compared with the final histology.

Results Some 127 women had both mammography and ultrasonographic imaging; the final grade was identical in 60 per cent. The positive predictive value of imaging reported as grade 5 or 4 combined with cytology of C5 or C4 was 100 per cent. All lesions with C3 cytology and benign imaging were benign on histological examination whereas if a C3 grade was combined with imaging grade 5 or 4, all the lesions were malignant.

Conclusion Combining the imaging grade with the results of aspiration cytology and clinical examination often predicts the final histology in patients with breast disease.

Clinical examination, radiological imaging and fine-needle aspiration cytology (FNAC) has become the approved method of assessing patients with symptomatic breast lumps[1–4]. The interpretation of cytological smears has become standard as described in the National Health Service (NHS) Breast Screening Programme guidelines for cytology procedures[5]. Similar standard prospectively evaluated categories for reporting of mammograms or breast ultrasonographic images do not currently exist. In some cases it may be very difficult for a clinician to assess the degree of radiological suspicion based on a written report, especially if the appearances are indeterminate. This study analyses the use of grades similar to those described for cytological analysis to report mammograms and ultrasonographic images.

Patients and methods

Some 306 consecutive new patients who presented over 12 months (September 1995 to August 1996) to the breast clinic at this hospital and subsequently underwent surgery were included in the study. Histological confirmation was obtained in all cases. The patients all underwent clinical examination and FNAC. Mammography was the imaging method in symptomatic women over 35 years. Patients under 35 years had high-frequency ultrasonography unless there was a strong clinical suspicion of cancer in which case a mammogram was also obtained. Most imaging was done on the day of presentation in the breast clinic; the radiologists were aware of the clinical findings but not the cytology results. The preoperative presumptive diagnosis was recorded.

Imaging

Mammography was carried out using a dedicated mammographic unit (International General Electric, Slough, UK) and film screen combination. Standard craniocaudal and lateral oblique views were taken, with further paddle magnification views in some cases before a final report was given. A Hitachi EUB 415 scanner (Wellingborough, UK) was used for ultrasonographic examination with a 7·5-MHz high-frequency transducer. The mammograms and ultrasonographic images were reported by one of three specialist breast radiologists. When ultrasonography was used to supplement mammography or vice versa, the radiologist was not blinded to the original imaging result. The grade for each imaging investigation was recorded independently using a scale M1–5 (mammography) or U1–5 (ultrasonography) (*Table 1*). If the findings on imaging were inconsistent, the most suspicious feature determined the final grade. Any additional mammographic views performed were included in the final grading.

Cytology

FNAC of palpable lesions was performed using a 21- or 23-G needle attached to a 10-ml syringe. Any nipple discharge was sent for cytology. FNAC of impalpable lesions was done using stereotactic or ultrasonographic control. The smears were air dried and fixed in alcohol, and then stained by both May–Gruenwald Giemsa and Papanicolaou techniques. A cytological grade was assigned using a scale C1–C5.

Analysis

The positive predictive values of abnormal cytology (C3–C5) and imaging were calculated according to published guidelines[5]. The sensitivity and specificity were also calculated. Atypical or indeterminate reports (grade 3) were evaluated both as a positive finding of malignancy and as a benign finding, resulting in two sensitivity and specificity rates for each modality of triple assessment. Inadequate aspirates were excluded from the sensitivity and specificity calculations for FNAC. Statistical analyses were carried out using Fisher's exact probability test.

Results

During the study, 311 breast lesions in 306 patients were excised; 150 were malignant (benign to malignant ratio 1:1). This excluded operations for nipple discharge. Fifty patients had lesions detected by mammographic screening; 47 from the NHS Breast Screening Programme and three from the Family History Clinic. There were 261 symptomatic lesions, including 230 palpable lumps and 16 patients with nipple discharge who underwent micro-

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Table 1 Grading of imaging reports

Grade	Degree of suspicion	Mammographic appearance	Ultrasonographic appearance
1	Normal appearance	No abnormality seen	No abnormality seen
2	Consistent with a benign lesion	Scar Well circumscribed mass of relatively low density possibly with halo and/or popcorn calcification Multiple well circumscribed rounded masses Lesion containing fat Ring or microcystic or diffuse bilateral calcification	Scar, implant, abscess, duct ectasia, haematoma Unilocular simple cyst Homogeneous well defined oval solid mass with horizontal orientation pushing surrounding tissues
3	Atypical or indeterminate appearance but probably benign	Distortion, possible positional shadow Localized cluster of round calcifications Solitary round mass of intermediate density	Cyst with solid elements or irregular wall Solid mass not clearly horizontally orientated Solid mass with a lobulated margin
4	Suspicious of malignancy	Ill defined or irregular dense mass Spiculated lesion without central mass Localized cluster of fine, punctate or granular calcification Lymphadenopathy alone	Ill defined heterogeneous mass Distortion with no central mass Lymphadenopathy alone
5	Consistent with malignancy	Spiculated lesion with central mass possibly with microcalcification Comedo calcification Thickened skin without a benign explanation All of above possibly with lymphadenopathy	Irregular hypoechoic mass interrupting breast trabeculae possibly with or without any of the following features: distortion, distal shadowing, vertical orientation and/or lymphadenopathy

When findings on imaging were mixed, the most suspicious finding determined the grade

Table 2 Sensitivity and specificity of the different modalities as part of the triple assessment

	Grades 3–5	Grades 4 and 5 only
FNAC (*n* = 252)		
Sensitivity (%)	98	94
Specificity (%)	83	95
Mammography (*n* = 249)		
Sensitivity (%)	92	83
Specificity (%)	78	91
Ultrasonography (*n* = 178)		
Sensitivity (%)	82	75
Specificity (%)	79	93

FNAC, fine-needle aspiration cytology

Table 3 Positive predictive value for malignancy of abnormal cytology, mammography and ultrasonography

	Positive predictive value (%)		
Investigation	Grade 3	Grade 4	Grade 5
Cytology (*n* = 146)	25	82	99
Mammography (*n* = 155)	48	74	99
Ultrasonography (*n* = 78)	25	70	94

dochectomy. The remainder presented with mastalgia or nipple symptoms but an incidental impalpable abnormality was detected radiologically and then excised. The sensitivity (proportion of cancers correctly identified) and the specificity (proportion of benign lesions correctly identified) were calculated for each modality of the triple assessment (*Table 2*).

Mammography

Mammography was performed in 249 patients. Seven cancers were reported as M1 and five as M2 giving an overall false-negative rate of 9 per cent. The false-negative rate was higher in patients aged less than 50 years (24 *versus* 4 per cent; P = 0·002). An indeterminate or M3 mammogram report had a positive predictive value for cancer of 48 per cent (*Table 3*). When M3 mammography was included as a positive finding, the sensitivity of mammography was 92 per cent overall (*Table 2*). Mammography was more sensitive in patients aged over 50 years (96 *versus* 77 per cent; *P* = 0·003), even if screen-detected lesions were excluded. Five women aged under 35 years with cancer had mammography. All lesions were reported as atypical or suspicious of malignancy; in one the ultrasonographic appearance was benign. Only one benign lesion, a radial scar, was reported as M5.

Ultrasonographic imaging

Fifty-one women (median age 28 years) had an ultrasonographic scan as their only imaging assessment; 48 lesions (94 per cent) were reported as normal or benign. If combined with a C2 FNAC result, all were benign on excision biopsy. Overall 178 women had ultrasonography. Five lesions reported as U1 were malignant, all of which were impalpable. If, however, a palpable lesion appeared normal on ultrasonography, it was benign. Seven cancers were reported as U2, of which three were impalpable. Overall the false-negative rate for ultrasonography was 18 per cent. Eight benign lesions were reported as U5 or U4. The histology included radial scars, fat necrosis and a phyllodes tumour. In all these cases the cytology was benign. Eight women with false-negative mammograms were assessed by ultrasonography, five of whom had lesions with malignant or suspicious features; two were reported as U3 and one as U2. Ultrasonographic imaging also helped to confirm the presence of a malignant lesion in five patients in whom the mammographic appearance was indeterminate (M3); however, a normal or benign ultrasonographic appearance did not exclude a malignancy when associated with an M3 mammogram. One hundred and twenty-seven women had both mammography and ultrasonography. The final grade given in the report was identical in 76 (60 per cent) and was identical or similar, i.e. M5 U4 or M5 U5, in 87 (69 per cent).

Cytology

FNAC was not performed in 16 patients for a variety of technical reasons such as the presence of an implant. The overall inadequate or C1 rate was 43 of 295 (15 per cent); 15 (10 per cent) of the 143 cancers on which FNAC was performed had inadequate (C1) cytology. A phyllodes tumour gave rise to the only false-positive C5 result. The smears were highly cellular and there was relative discohesion of the epithelial component. In this patient, imaging was indeterminate (M3, U3). Three cancers were reported as C2 giving a false-negative rate of 2 per cent.

Scoring system

Table 4 shows the relationship of the FNAC and imaging results with the final histology. If a patient had both methods of imaging, each report was regarded separately and the most suspicious used. Excluded from this *Table* were 43 lesions with C1 cytology and 21 lesions for which there was no imaging or FNAC result. The positive predictive values of C5 and C4 cytology were 99 and 82 per cent respectively. All 103 lesions graded C5 or C4 by FNAC and grade 4 or 5 by mammography or ultrasonography were malignant. A C3 grade on FNAC had a positive predictive value for cancer of 25 per cent. When combined with a benign imaging result, the positive predictive value was 0 per cent, compared with 100 per cent when combined with suspicious or malignant imaging ($P = 0 \cdot 0003$). All lesions of imaging grade 3 when associated with C2 cytology were benign ($n = 14$). Likewise, all lesions with C2 cytology and benign or normal appearances on imaging ($n = 79$) were benign when excised.

Table 4 Relationship between fine-needle aspiration cytology (C1–5) and mammography (M1–5) and/or ultrasonographic imaging (U1–5) grade and final histology

Combined cytology and imaging (M/U) grade	Benign	Cancer	Positive predictive value (%)
Benign			
C3 and M/U 1 or 2	12	0	0
C2 and M/U 1, 2 or 3	93	0	0
Indeterminate			
C5 + C4 and M/U 1, 2 or 3	6	13	68
C4 and M/U 4	0	5	100
C2 and M/U 4 or 5	9	3	25
C3 and M/U 4 or 5	0	5	100
C3 and M/U 3	3	0	0
Malignant			
C5 and M/U 4 or 5	0	81	100
C4 and M/U 5	0	17	100

Discussion

Clinical examination, FNAC and imaging (mammography and/or ultrasonography) combined as the triple assessment for breast abnormalities has a sensitivity of greater than 99 per cent if all investigations concur[3]. When there are discrepancies a definitive diagnosis cannot be made and excision of the lesion is often recommended[3,6]. The scoring system described here resulted in sensitivity and specificity rates comparable to previously published data[3,7]. By combining the imaging grades with the FNAC results, the final histology can be predicted in the majority of cases (*Table 4*), potentially reducing the need for biopsy.

There is still a widespread tendency amongst surgeons to remove all discrete lumps in women aged over 35 years, despite a normal triple assessment, because of the small but significant false-negative rate. All 79 lesions in this study with benign cytology and imaging were benign on histological examination. Six were clinically suspicious but the remainder were thought to be benign on examination; 39 (53 per cent) were in women aged over 35 years. Had these lesions not been excised the rate of benign biopsy could have been reduced by 45 per cent and the benign to malignant ratio to 1:2.

Lesions with atypical cytology (C3), when associated with benign imaging were all benign on excision; similarly lumps with atypical imaging (M3 or U3), when associated with benign cytology were all found to be benign (*Table 4*). This indicates that if a patient does not wish surgery and the lesion is clinically benign, conservative treatment is safe, providing follow-up is adequate with repeat FNAC or imaging as appropriate.

A C5 or C4 result on FNAC combined with suspicious or malignant imaging (M4–5 and/or U4–5) had a positive predictive value for cancer of 100 per cent, suggesting that definitive treatment can be planned for clinically suspicious lumps with these results (*Table 4*). If the FNAC result is C5 or C4 but the imaging indicates a benign lesion, or vice versa, then a core biopsy should be performed or the lump excised.

Over two-thirds of the patients (69 per cent) who had both mammography and ultrasonography had identical or similarly graded reports for both imaging methods. This demonstrates a close correlation between the two techniques but also suggests that in the majority of cases ultrasonographic imaging in addition to mammography may not be necessary, especially if the mammogram is reported as definitely malignant (M5) or definitely benign (M2).

In conclusion, this imaging scoring system accurately relays the radiologist's suspicions to the clinician. The combination of the imaging grade with the results of aspiration cytology and clinical examination helps predict the final histology. The value of this scoring system needs to be confirmed in larger prospective studies.

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Effect of graft reperfusion on intracellular calcium levels in mononuclear leucocytes during human orthotopic liver transplantation

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Background Orthotopic liver transplantation (OLT) is accompanied by local and systemic manifestations of the ischaemia–reperfusion syndrome. Local effects are mediated in part through changes in intracellular calcium levels in Kupffer cells. Arachidonic acid metabolites mediate increases in intracellular calcium concentration and thus potentiate the effect of free radicals. This study was carried out to characterize white blood cell (WBC) calcium changes as a mediator for white cell activation in human OLT.

Methods Twenty consecutive patients had OLT using standard surgery and anaesthesia techniques. Blood samples were drawn for estimation of WBC cytosolic calcium content at induction of anaesthesia, 5 min before graft reperfusion and 15 min after reperfusion. The rate of rise in intracellular calcium concentration after the addition of a calcium chloride 1 mmol l^{-1} solution to the extracellular milieu was used as an estimate of membrane calcium permeability.

Results Both extracellular ($P = 0{\cdot}0002$) and intracellular ($P = 0{\cdot}0008$) calcium concentrations rose with time. However, at no time was there a correlation between extracellular and intracellular calcium levels or rate of calcium influx ($r^2 = 0{\cdot}002$, $P = 0{\cdot}78$). There was a significant increase in intracellular calcium concentration ($P = 0{\cdot}0008$) and in the rate of rise of intracellular calcium levels ($P = 0{\cdot}0009$) after reperfusion.

Conclusion There was a significant increase in circulating monocyte membrane permeability for calcium and cytosolic calcium concentration following reperfusion in human OLT. This was independent of extracellular calcium concentration. These results are consistent with WBC activation by reperfusion and could be implicated in the systemic reperfusion syndrome seen in OLT in humans.

Orthotopic liver transplantation (OLT) is associated with a reperfusion syndrome[1], which occurs soon after revascularization of the ischaemic donor graft. Post-reperfusion syndrome is defined[1] as a reduction in mean arterial pressure of 30 per cent occurring within 5 min of graft reperfusion and persisting for at least 1 min. This may be cytokine mediated and is associated with changes in arachidonic acid metabolism. Hypotension associated with a low systemic vascular resistance may persist for 1 h or more. Reperfusion syndromes are thought to be mediated via intracellular calcium influx resulting in raised cytosolic calcium concentration[2-4]. Previous studies have focused on intracellular calcium concentration change in graft cells following reperfusion. However, the reperfusion syndrome exhibits systemic manifestations. Therefore, in this study the extent to which reperfusion of donor liver graft is associated with changes in intracellular calcium concentration in mononuclear leucocytes was characterized, reflecting the systemic nature of the reperfusion syndrome.

Patients and methods

The study was approved by the local research ethics committee and informed consent obtained. Twenty consecutive patients who had elective OLT were studied. All the patients were anaesthetized using an opioid–volatile agent sequence with venovenous bypass according to a standard technique[5]. Non-invasive monitoring was established and anaesthesia induced with midazolam 0·1 mg kg^{-1}, alfentanil 0·1 mg kg^{-1} and atracurium 0·6 mg kg^{-1}. Following tracheal intubation the lungs were ventilated to normocapnia with desflurane in oxygen-enriched air. Anaesthesia was supplemented[6] with alfentanil at 0·05 mg kg^{-1} h^{-1} and muscle relaxation facilitated with atracurium 0·5 mg kg^{-1} h^{-1}. Further monitoring included a triple-lumen central venous line, mixed venous oximetric right-ejection fraction pulmonary artery flotation catheter, and a radial arterial line. An 18-Fr percutaneous cardiac bypass cannula was inserted into the internal jugular vein and connected to a rapid infusion system (Hemonetics, Braintree, Massachusetts, USA)[7]. A further 18-Fr bypass cannula was placed into the right femoral vein to allow venovenous bypass[8]. Dopamine 3 μg kg^{-1} min^{-1} and 4 per cent glucose in 0·18 per cent saline infusions (1 ml kg^{-1} h^{-1}) were commenced and continued after operation according to the authors' protocol[5]. Standard surgical technique was used[9] with an out-of-ice to reperfusion time of less than 1 h in all cases. Reperfusion sequence involved removal of the upper caval clamp, portal vein reperfusion, removal of the lower caval clamp and subsequent hepatic arterial anastomosis. No drugs that might have affected extracellular calcium levels were given between stages I and II; between stages II and III, calcium supplements were used to maintain serum ionized calcium concentration between 0·85 and 1·4 mmol l^{-1} and the dose was recorded. Immunosuppressant therapy was withheld until after surgery.

Blood samples (10 ml) for determination of intracellular calcium concentration ($[Ca^{2+}]_i$) were drawn into lithium–heparin bottles at three time points: induction of anaesthesia (stage I), 5 min before reperfusion of the graft (stage II) and 15 min after reperfusion (stage III). The anticoagulated blood was mixed with equal volumes of white blood cell culture medium RPMI 1640 (Sigma Diagnostics, St Louis, Missouri, USA)[10] at pH 7·3. The blood mixture was then layered on to Histopaque-1077 (Sigma Diagnostics), which is a solution of polysucrose and sodium diatrizoate, and centrifuged at 700*g* for 30 min at room temperature. During centrifugation, erythrocytes and granulocytes are aggregated by the polysucrose and sediment rapidly, but lymphocytes and other mononuclear cells remain at the

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plasma–Histopaque interface. The mononuclear layer was then collected before $[\mathrm{Ca}^{2+}]_i$ determination.

$[\mathrm{Ca}^{2+}]_i$ was measured using the fluorescent dye, Fura-2, employing established methods[11]. Fura-2 is a fluorescent indicator whose peak emission wavelength changes from 380 to 340 nm when it is bound to Ca^{2+} in a 1 : 1 ratio. The cell-permeant acetoxymethylester form of Fura-2, Fura-2AM (Sigma Diagnostics), was incubated with the cells at a concentration of 1 mmol l^{-1} for 30 min at 37°C. After incubation, cells were collected by centrifugation and washed twice with RPMI 1640 solution. After the final wash, cells were resuspended in RPMI 1640 before determination of $[\mathrm{Ca}^{2+}]_i$.

The fluorescence measurements were performed at 25°C using a luminescence spectrophotometer (LS50; Perkin Elmer, Beaconsfield, UK). The excitation wavelengths were 340 and 380 nm, and the emission wavelength was 510 nm. Emission intensities after alternate excitation at 340 and 380 nm were plotted as a 340/380 ratio (R), and an average of 30 readings over 60 s was obtained for each sample. A value for the maximum ratio ($\mathrm{R}_{\max}$) was obtained by adding calcium chloride 1 mmol l^{-1} to the milieu, then disrupting the cells using the ionophore Ionomycin (ICN Biomedicals, Thame, UK), the ratio being that for completely bound Fura-2. The minimum ratio ($\mathrm{R}_{\min}$) was then derived by adding manganese chloride 1 mmol l^{-1}, which displaces Ca^{2+} from Fura-2 and gives a ratio value for completely unbound probe. $[\mathrm{Ca}^{2+}]_i$ was calculated using the Grynkiewicz formula[11]. Following addition of calcium chloride to the extracellular milieu, the initial rate of rise in $[\mathrm{Ca}^{2+}]_i$ was recorded. This was compared between cells collected before and after graft reperfusion.

Plasma ionized (extracellular) Ca^{2+} levels were also measured at the same time as samples for $[\mathrm{Ca}^{2+}]_i$ determination, using a Model 288 blood gas system (Ciba-Corning, Medfield, Massachusetts, USA). All measurements were performed in duplicate to avoid idiosyncratic errors, and mean values were recorded.

Statistical analysis

Results are expressed as median (interquartile range). Determinations of $[\mathrm{Ca}^{2+}]_i$ at induction and before and after reperfusion were compared using Friedman's two-way analysis of variance by rank for non-parametric data. Specific differences between the time points were investigated using a Bonferroni-corrected Wilcoxon signed-rank matched-pairs test. The rate of rise of $[\mathrm{Ca}^{2+}]_i$ before and after reperfusion was compared with the Wilcoxon signed-rank matched-pairs test. Correlations between intracellular and extracellular calcium concentration, and rate of rise of intracellular calcium content, were tested by Pearson's linear regression.

Results

The patients were seven men and 13 women of mean age 49 (range 42–50) years. Their diagnoses were: primary biliary cirrhosis (five patients), seronegative hepatitis (three), primary sclerosing cholangitis (one), lupus (one), chronic rejection (one), alcoholic cirrhosis (three), hepatitis B (one) and cryptogenic cirrhosis (five). Graft total ischaemic times were 592 (540–710) min. Total calcium administered to maintain extracellular calcium concentration within the range 0·85–1·4 mmol l^{-1} was 22·5 (20–30) mmol.

Intracellular and serum (extracellular) ionized calcium concentrations and the rate of rise of intracellular calcium content in the experimental rig (calcium influx) are detailed in *Table 1*. Both extracellular ($P = 0·0002$) and intracellular ($P = 0·0008$) calcium concentrations rose with time. However, at no time was there a correlation between extracellular and intracellular calcium concentration (*Fig. 1*) or rate of calcium influx ($r^2 = 0·002$, $P = 0·78$).

Table 1 Extracellular and intracellular free calcium concentrations and rate of rise of cytosolic calcium level

	Baseline (I)	Before reperfusion (II)	After reperfusion (III)
Extracellular calcium (mmol l^{-1})	1·06 (0·92–1·15)	1·14 (0·9–1·24)*	1·42 (1·31–1·62)
Intracellular calcium (nmol l^{-1})	10·8 (6·4–23·1)	16·7 (8·2–27·0)	24·9 (16·2–50·0)†
Calcium influx (nmol $\mathrm{l}^{-1}\,\mathrm{s}^{-1}$)	—	7·4 (4·6–13·5)	8·9 (5·7–33·3)‡

Values are median (interquartile range). *$P = 0·0002$ *versus* baseline and postreperfusion; †$P = 0·0008$, ‡$P = 0·0009$ *versus* before reperfusion (Bonferroni-corrected Wilcoxon signed rank test)

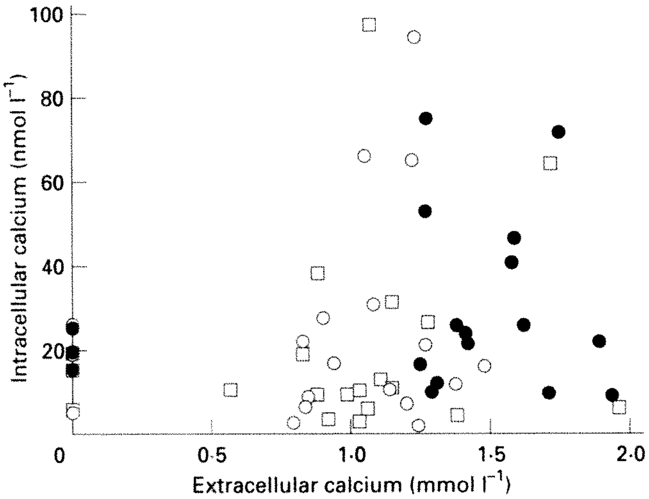

Fig. 1 Intracellular *versus* extracellular calcium concentrations. No correlation was seen between extracellular and intracellular calcium levels at the three time points: □, baseline (I) ($r^2 = 0·02$, $P = 0·57$); ○, before reperfusion (II) ($r^2 = 0·001$, $P = 0·89$); ●, after reperfusion (III) ($r^2 = 0·04$, $P = 0·44$)

There was an increase in median $[\mathrm{Ca}^{2+}]_i$ between times I and II but this was not statistically significant ($P = 0·46$). There was a significant increase in $[\mathrm{Ca}^{2+}]_i$ ($P = 0·0008$) and rate of rise of $[\mathrm{Ca}^{2+}]_i$ ($P = 0·0009$) after reperfusion. A correlation was observed between $[\mathrm{Ca}^{2+}]_i$ and rate of influx ($r^2 = 0·42$, $P < 0·001$) (*Fig. 2*). Ischaemic time was not a predictor for postreperfusion $[\mathrm{Ca}^{2+}]_i$ ($P = 0·84$). There was a trend, which was not statistically significant, for patients with a long graft ischaemic time to show a greater rise in $[\mathrm{Ca}^{2+}]_i$ between times II and III ($r^2 = 0·26$, $P = 0·094$).

Discussion

In these patients undergoing elective liver transplantation, graft reperfusion was associated with a significant rise in $[\mathrm{Ca}^{2+}]_i$ in mononuclear leucocytes. Coincidentally an increase in serum ionized (extracellular) calcium concentration was observed during the operation. This probably related to calcium administration as part of the anaesthetic technique[12]. The increase in $[\mathrm{Ca}^{2+}]_i$ did not appear to correlate with changes in serum ionized calcium level. However, when postreperfusion cells were

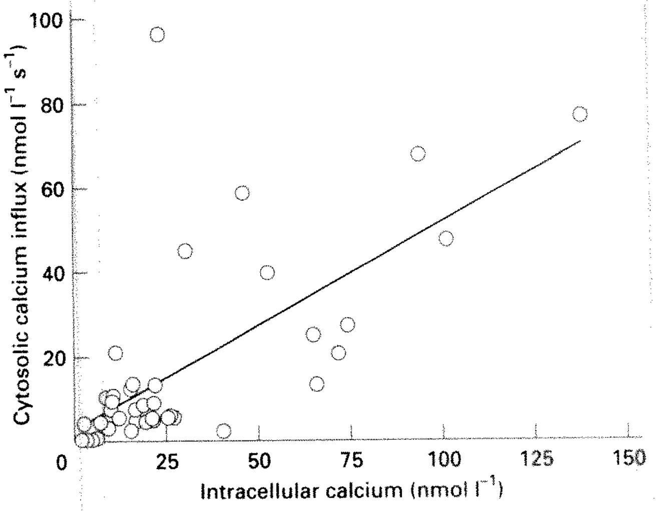

Fig. 2 Correlation between intracellular calcium concentration after reperfusion and cytosolic calcium influx under experimental conditions ($r^2 = 0{\cdot}42$, $P < 0{\cdot}001$)

compared with prereperfusion cells, they not only had a higher cytosolic calcium level, but in the test rig showed a greater rate of increase of $[Ca^{2+}]_i$ when the Ca^{2+} concentration in the test milieu was varied. Small changes in membrane calcium influx could lead to increased mobilization of intracellular calcium stores and hence a substantial increase in cytosolic free calcium.

An increase in $[Ca^{2+}]_i$ has been implicated in several models of ischaemia–reperfusion injury[2–4,13]. The mechanisms may include complex changes in intracellular activation of the phospholipase system and an increase in membrane calcium permeability, as dihydropyridine-type calcium channel antagonists block the increase in $[Ca^{2+}]_i$ following ischaemia–reperfusion injury in the hepatic Kupffer cell[14]. There is circumstantial evidence that this may also be true of the circulating monocyte[15,16].

The reperfusion syndrome in liver transplantation is well recognized[1], occurring to a significant extent in nearly every transplant, as reflected by high serum transaminase levels in the first few days after operation. In the worst cases this can lead to primary graft failure and death[17].

Reperfusion syndrome is thought to begin as a local effect due to Kupffer cell activation in the graft[18]. Storage of donor liver graft with calcium channel blockers reduces Kupffer cell $[Ca^{2+}]_i$ and improves graft survival[19].

The local effects are accompanied by a systemic disorder, involving release of inflammatory mediators[20] and increased circulating levels of arachidonic acid and its derivatives[21]. Arachidonate increases $[Ca^{2+}]_i$ in isolated perfused Kupffer cells in a dose-dependent manner[22]. In another recent study[23], primary cultures of rat Kupffer cells liberated significant amounts of prostaglandin (PG) D_2, PGE_2 and thromboxane (measured as thromboxane B_2) when exposed to reoxygenation after 4 h of hypoxia. Raised prostanoid synthesis was preceded by increased $[Ca^{2+}]_i$.

In the present study it was demonstrated that the increased $[Ca^{2+}]_i$ following reperfusion of the graft was not localized to Kupffer cells, but seen systemically in other cell populations within the immune system. This is consistent with previous findings of systemic changes in arachidonic acid metabolism, autacoid and adhesion molecule expression[20,21]. Calcium is an important intracellular messenger involved in signal transduction and white cell activation. It is proposed that changes in $[Ca^{2+}]_i$ in mononuclear leucocytes are implicated in the systemic immune response seen following liver graft reperfusion in humans.

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Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland

The Journal apologizes for omitting the following abstracts which should have been published in the March 1998 issue.

Preoperative decompression of an obstructed biliary tree does not increase the incidence of postoperative sepsis

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Aim To assess the incidence of infected bile in patients with preoperative biliary decompression and its role in the development of septic complications and biliary fistula after preoperative drainage of the bile duct.

Methods A total of 128 patients (81 men, 47 women) underwent hepaticojejunostomy Roux-en-Y with or without resection of the pancreatic head for either benign disease ($n=46$) or some type of pancreatic or periampullary carcinoma ($n=82$). Preoperative biliary decompression was carried out in 63 patients by the endoscopic ($n=45$), transhepatic ($n=11$) or surgical ($n=7$) route; 65 had no such drainage. Bile cultures were obtained from the bile duct at operation in every case. Operations were performed under broad-spectrum antibiotic cover.

Results Positive cultures were obtained in 55 of 63 patients with preoperative drainage as opposed to 18 of 65 patients without drainage ($P=0{\cdot}0001$). A median of two different organisms (range 1–3) were grown (coliforms 37, enterococcus 16, pseudomonas 8), especially in patients with an indwelling stent. However, the presence or absence of bacterobilia did not affect the incidence of postoperative septic complications (21 *versus* 22 per cent, $P=0{\cdot}9$, or 12 *versus* 13 per cent if chest infection is excluded) nor yet the incidence of anastomotic biliary leakage (5·7 *versus* 7 per cent, $P=10$).

Conclusion Although preoperative biliary decompression nearly always contaminates the biliary tree, it does not increase the risk of postoperative sepsis or biliary fistula in the presence of antibiotic prophylaxis.

Laparoscopic cholecystectomy under epidural anaesthesia in patients with chronic respiratory disease

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Aim Laparoscopic cholecystectomy (LC) has become firm established as the procedure of choice for gallstone disease that usually necessitates general anaesthesia and endotracheal intubation to prevent aspiration and respiratory embarrassment secondary to the induction of pneumoperitoneum. There is a paucity of data in the literature on the procedure being performed under regional (epidural) anaesthesia, especially in patients with significant pulmonary disease who are deemed high risk for general anaesthesia. This report describes preliminary experience with LC using epidural anaesthesia in patients with chronic obstructive pulmonary disease (COPD).

Methods LC was performed in six patients (one man, 5 women), median age 56 (range 38–74) years, under epidural anaesthesia over an 8-month period. All patients were American Society of Anesthesiologists grade 3 or 4 and the mean FEV_1/FVC was 0·52 (range 0·4–0·68), due to chronic asthma (two) and COPD (four). They were admitted 1 day before surgery for pulmonary function tests, nebuliser and chest physiotherapy. An epidural catheter was introduced at T10/11 intervertebral space and a bolus of 0·5 per cent bupivacaine was administered. Depending on the patient's pain threshold and the segmental level of analgesia achieved, incremental doses of 2 ml of 0·5 per cent bupivacaine along with boluses of intravenous 100 mcg Fentanyl were given to each patient. The patients were breathing spontaneously, no nasogastric tube was inserted and the pneumoperitoneum pressure was limited to 10 mmHg. LC was performed using a standard technique.

Results All patients tolerated the procedure well and made an uneventful postoperative recovery. Median operating time was 50 min and mean length of hospital stay was 2·5 (range 2–4) days. The epidural catheter was removed the morning after operation and only one patient required postoperative opioid analgesia. Two patients complained of persistent shoulder-tip pain during surgery and required intraoperative analgesia. There was no change in the patients' cardiorespiratory status including pO_2 and pCO_2, and no complications occurred either intraoperatively or postoperatively.

Conclusions LC can be performed safely under epidural anaesthesia in patients with severe COPD. Intraoperative shoulder-tip or abdominal pain does not seem to be a major deterrent and can be controlled effectively with small doses of opioid analgesia

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Experimental study of acid burden and acute oesophagitis

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Background The relationship of the pH of oesophageal refluxate and its pepsin content to injury of oesophageal mucosa remains unclear. A study was made of the earliest morphological alterations in the oesophageal mucosa secondary to varying concentrations of hydrochloric acid with or without pepsin.

Methods Adult cats had varying concentrations of acid with and without 1 per cent porcine pepsin infused into the oesophagus through a paediatric feeding tube placed 5 cm above the oesophagogastric junction at a rate of 1 ml/min for 30 min. At autopsy 24 h later, the oesophagus was removed intact and scored by an expanded modification of a previously published histopathological scoring system. This included estimates of the intensity and distribution of four morphological features: basal cell hyperplasia (BCH), intraepithelial leucocytes (IELs), subepithelial leucocytes and ulcers. Each of these four categories was scored from 0 to 4, with a maximum injury score of 16.

Results Mean(s.e.m.) scores were as follows: pH 1, 15·0(1·0); pH 1 with pepsin, 13·3(1·4); pH 2, 15·3(0·7); pH 2 with pepsin, 11·7(1·1); pH 3, 1·8(1·6); pH 3 with pepsin, 3·7(1·9); pH 4 with or without pepsin, 0·6(0·2). Differences between pH 3 and 4 *versus* pH 1 and 2 were significant ($P < 0·05$).

Conclusion Injury to the oesophagus is more dependent on the pH of refluxate than on the presence of pepsin. Peptic injury appears to occur at a critical threshold of acid burden ($pH < 3$) as opposed to a graded level of injury based on a pH scale.

For decades the pathophysiology of reflux oesophagitis has been elusive. Although gastro-oesophageal reflux disease (GORD) is the most common upper gastrointestinal disease in the Western world, only a small proportion of the population at risk develops reflux oesophagitis and even fewer demonstrate evidence of macroscopic disease[1]. Many mechanisms of defence act as important deterrents to GORD, all of which in combination maintain a stable milieu within the distal oesophagus and help to prevent reflux injury[2].

In vivo studies in animals have demonstrated that not only acid but also pepsin, bile and pancreatic enzymes (as components of gastroduodenal contents) can induce varying degrees of oesophagitis independently[3–7]. Separation of the roles of acid and pepsin in the production of oesophagitis is difficult because pepsin is active only in an acid environment. Although the presence of acid with or without pepsin remains the *sine qua non* for the development of oesophagitis, the precise relationship of the pH of refluxate to mucosal injury remains unclear. The ulcerogenic potentials of acid and pepsin have been described previously[8,9]; however, there is a paucity of data available on the quantitative evaluation of the effect of varying concentrations of acid to induce oesophagitis. These experiments were designed to quantitate the earliest morphological alterations in the oesophageal mucosa secondary to infusions of different concentrations of hydrochloric acid with and without pepsin.

Materials and methods

Adult cats weighing 3–5 kg were studied. Water and food were permitted *ad libitum* and the animals were not fasted before infusion. Anaesthesia was induced with a combination of ketamine hydrochloride 15 mg/kg and acepromazine 0·2 mg/kg administered intramuscularly. All cats underwent upper endoscopy (Olympus GIF-X20 Endoscope; Olympus, Tokyo, Japan) before infusion, to exclude any gross abnormality of the oesophageal mucosa and also to locate the oesophagogastric junction. The animals were positioned lying on their left side with their head elevated at a slight angle (10–15°). A Harvard infusion pump was used to deliver hydrochloric acid at a rate of 1·0 ml/min through a paediatric feeding tube placed 5 cm above the endoscopically located oesophagogastric junction. Varying pH concentrations of hydrochloric acid (pH 1 to pH 4) with and without 1 per cent porcine pepsin (Sigma Chemicals, St Louis, Missouri, USA) were infused in random order for 30 min in different animals on different experimental days. Most of the authors' previous work studying acute oesophagitis in a feline model has been done using either 0·8 or 1 per cent pepsin. Because human gastric juice normally contains 1500–2000 units/ml of pepsin and porcine pepsin usually contains 2500–3500 units/mg at pH 1, concentrations of pepsin used to reproduce physiological conditions should be 1 mg/ml (1 per cent) or less[4].

Five or six cats were randomly assigned to each study group as shown in *Table 1*. An additional control group of six cats was included to ascertain whether intraoesophageal infusion of saline might affect the oesophageal epithelium. All animals were allowed food and drink *ad libitum* after recovery from anaesthesia at the end of the procedure. Analgesia in the form of Buprenorphine 0·2–0·4 mg/kg was administered subcutaneously to all animals, including controls. All the cats were killed 24 h after the infusion using intravenous sodium pentobarbital 100 mg/kg and the oesophagus was removed intact along with the proximal portion of the stomach. Each specimen was opened

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longitudinally, pinned to a cork board, and fixed overnight in 10 per cent buffered formalin. The entire distal 5 cm of the oesophagus was processed routinely for histological examination, with longitudinal sections stained with haematoxylin and eosin and evaluated by a pathologist unaware of the treatment sequences.

Each oesophagus was examined and scored by an expanded modification of the scoring system described previously[10]. Briefly, the specimens were scored for basal cell hyperplasia (BCH), intraepithelial leucocytes (IELs), subepithelial leucocytes (SELs) and the presence or absence of ulcers. BCH was defined as the ratio of basal cell layer thickness to total mucosal thickness. Measurements of the thickness of the basal cell layer and total mucosa were performed with an ocular micrometer and BCH was scored as follows: 0, less than 15 per cent; 1 +, 15–40 per cent; 2 +, more than 40 per cent. IELs were scored as number per high-power field (HPF): 0, none; 1 +, 1–2 per HPF; 2 +, more than 2 per HPF. SELs were scored as: 0, none; 1 +, 1–4 per HPF; 2 +, 5 or more per HPF. The distribution or linear extent for BCH, IELs and SELs was assayed as: 0, no abnormality or abnormalities present in a single microscopic focus; 1, one to four foci; 2, more than four foci or diffuse changes. Such microscopic foci had to be distanced physically from similarly affected foci. Thus a combined (degree plus extent) score of 0–4 was possible for each of these parameters. An ulcer was defined as a full-thickness area of epithelial destruction; if none was present, then the ulcer score was 0. When a solitary ulcer was present, the score was 2. When two or more physically discrete ulcers were present in the examined segment, a score of 4 was given. For all specimens, scoring was performed on the most severely affected foci. However, IELs, SELs and BCH were not evaluated within three HPFs of an ulcer. The scores for BCH, IELs, SELs and ulcers were added, so that each cat obtained a total oesophagitis score of 0–16. This scoring system was developed as the result of consideration of histological changes seen in human reflux oesophagitis and in preliminary studies in the cat[9,11].

Statistical analysis

Differences between mean total histology scores were analysed using one-way analysis of variance. If the *F* ratio indicated a significant difference, the Newmann Keuls *post hoc* test was used to identify individual differences between groups. Statistical significance was set at the 0·05 level.

Results

The mean cumulative histology scores following various infusions of acid with and without pepsin are shown in *Table 1*. In the group of animals that received hydrochloric acid alone at a concentration of either 0·1 mol/l (pH 1) or 0·01 mol/l (pH 2), all but one had extensive injury and hence a maximum score of 16. Although these specimens demonstrated extensive ulceration (grade 4), the number and size of ulcers varied from animal to animal. Addition of pepsin at pH 1 or 2 caused a more variable response in the oesophagus, with total scores ranging from 8 to 16 (mean 13·3) and from 7 to 14 (mean 11·7) respectively. Differences between total histology scores at pH 1 and 2 with or without pepsin were not statistically significant. Following infusion of hydrochloric acid 0·001 mol/l (pH 3), there was a sharp reduction in injury to the oesophageal mucosa when compared with lower pHs (*Fig. 1*). There was no evidence of any mucosal injury in the saline control animals (*Fig. 2*).

Table 1 Histology scores following various infusions of acid with and without pepsin

Groups	pH	No. of animals	Mean(s.e.m.) score
Control		6	0
HCl 0·1 mol/l	1	5	15·0(1·0)
HCl 0·1 mol/l + pepsin	1	6	13·3(1·4)
HCl 0·01 mol/l	2	6	15·3(0·7)
HCl 0·01 mol/l + pepsin	2	6	11·7(1·1)
HCl 0·001 mol/l	3	6	1·8(1·6)*
HCl 0·001 mol/l + pepsin	3	6	3·7(1·9)*
HCl 0·0001 mol/l	4	6	0·5(0·2)†
HCl 0·0001 mol/l + pepsin	4	6	0·7(0·3)†

**P* values compared by ANOVA between groups. HCl, hydrochloric acid. **P* = 0·01, †*P* < 0·05 (pH 3 and 4 *versus* pH 1 and 2, analysis of variance)

Detailed results after exposure to a specific concentration of acid are described below.

With pH 1, all cats except one had extensive ulceration, both macroscopic and histological, and therefore had a maximum cumulative score of 16. Some 24 h after a 30-min acid exposure, the number and size of ulcers varied from animal to animal. The mean score in this group was 15 (range 11–16) (*Fig. 3*).

For pH 1 plus pepsin, addition of pepsin in the hydrochloric acid 0·1 mol/l infusion produced a slightly more variable response in the animals, with histological scores varying from 8 to 16 (mean 13·3). Three of six cats in this group had extensive ulceration and inflammation, with a cumulative score of 16.

At pH 2, the mucosa was severely damaged (leading to ulcers) in five of six animals following the acid infusion,

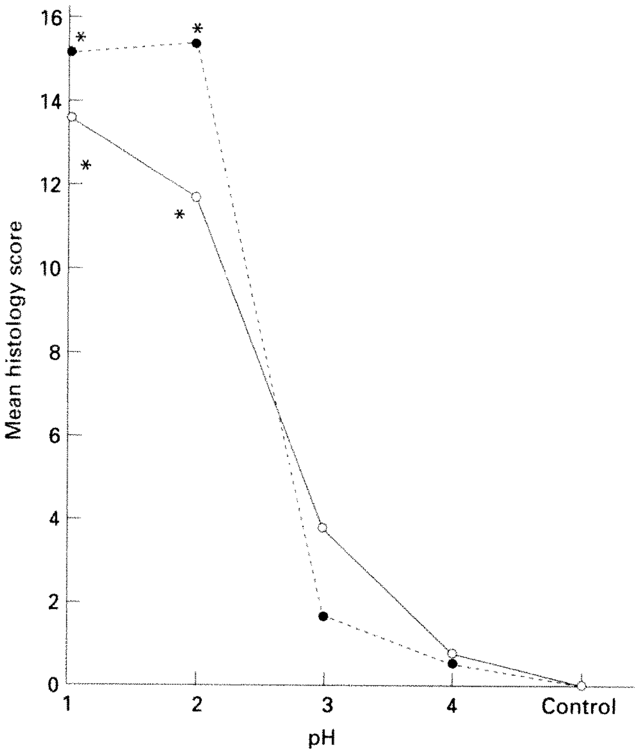

Fig. 1 Histology score at different pH values with (●) or without (○) pepsin. A sharp decline in oesophageal mucosal injury is seen at pH 3, compared with that at pH 1 and 2, with almost no injury at pH 4. Peptic activity appears to be more pronounced at pH 3 than at pH 2. **P* < 0·05 *versus* pH 3 and 4 (analysis of variance)

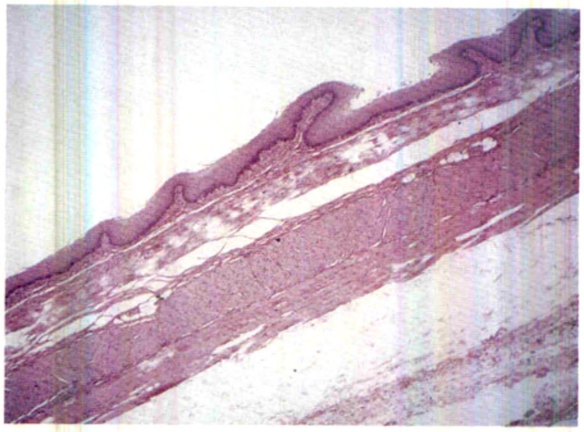

Fig. 2 Saline control cat. Note intact squamous epithelium with thin basal cell layer occupying less than 15 per cent of the mucosal thickness, and unremarkable submucosa and muscularis propria. There is complete lack of inflammation and no layer of keratin. This specimen attained a score of 0. (Haematoxylin and eosin stain; original magnification ×20)

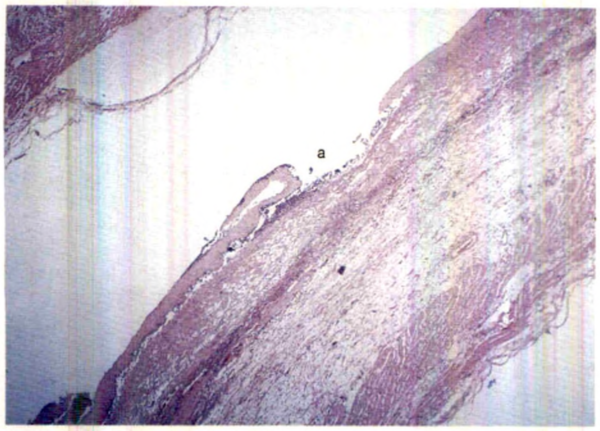

Fig. 3 Microscopic lesions from one study cat. Note the ulcer (a) with prominent mural damage, sloughing of the necrotic mucosa, transmural inflammation and prominent oedema in all the layers typically seen after a 30-min infusion of acid at pH 1 and 2. This specimen attained a maximum score of 16. (Haematoxylin and eosin stain; original magnification ×20)

each attaining a maximum score of 16. The animal in this group without ulcer had a score of 12.

With pH 2 plus pepsin, mucosal injury was much more variable after infusion of hydrochloric acid 0·01 mol/l containing 1 per cent pepsin and the animals had a mean score of 11·7 (range 7–14).

At pH 3, minimal histological changes (early BCH) were identified following infusion of hydrochloric acid 0·001 mol/l. The mean histological score was 1·8 (range 0–10). At autopsy, no gross macroscopic changes were seen in the distal oesophagus in any animal.

With pH 3 plus pepsin, injury was more evident when pepsin was added to hydrochloric acid 0·001 mol/l, with a mean score of 3·7 (range 0–11) (*Fig. 4*).

For pH 4 with or without pepsin, there was no gross or microscopic evidence of injury to the oesophagus in any animal except one, after infusion of hydrochloric acid 0·0001 mol/l with or without pepsin. One cat in each group (with and without pepsin) showed minimal SELs and IELs such that each attained a score of 3 and 4 respectively.

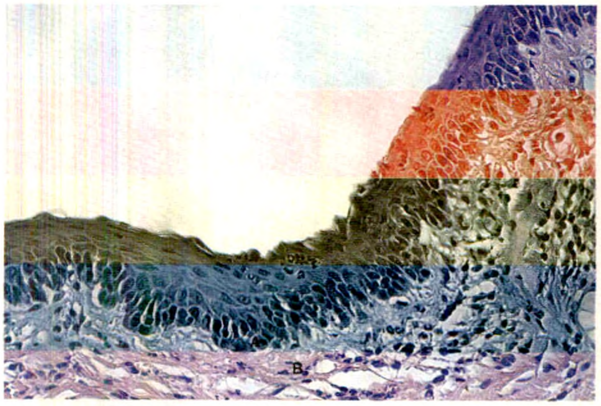

Fig. 4 Oesophageal mucosa after infusion of acid at pH 3 with pepsin. Note the intraepithelial leucocytes (A), subepithelial leucocytes (B) and basal cell hyperplasia (C). This specimen attained a score of 8. (Haematoxylin and eosin stain; original magnification ×40)

Discussion

The oesophageal mucosa is exposed repeatedly to potentially damaging substances both by ingestion and by reflux of noxious gastric contents. These may contain hydrochloric acid as well as pepsin, bile and pancreatic enzymes. *In vivo* studies have shown that each component of the refluxate may induce oesophageal mucosal injury to a greater or lesser degree[5–7]. Various studies support the concept of an 'oesophageal mucosal barrier' which exists in the normal state and is relatively impermeable to luminal acid, thus preventing injury[12,13]. Lillemoe *et al.*[4] showed that disruption of this barrier cannot be equated with pathological injury and that different components of the gastroduodenal contents may have different sites or mechanisms of injury. The development of oesophagitis depends on the duration, frequency, volume and virulence of the refluxed material, the effectiveness of the clearing peristalsis and the resilience of the exposed oesophageal mucosa.

Previous *in vitro* experiments have shown that the optimum pH for pepsin-catalysed reactions is between 1·5 and 2·5[8,14,15]. One experimental study confirmed that the most severe injury to feline oesophageal mucosa occurred between pH 1 and pH 2 as a result of protein denaturation secondary to 'oesophageal burn' caused by the high acid concentration. The addition of pepsin at such a low pH did not increase the severity of injury. At pH 2·5 the injury was more pronounced by the addition of pepsin, possibly due to protein digestion caused by the enzymatic activity of pepsin[8]. Another *in vitro* study[16] suggested that serosal acidification was more damaging than mucosal acidification, indicating that the acid entered the paracellular pathway and the hydrogen ions traversed the basolateral membrane more readily than the mucosal membrane. In a semiquantitative study, Redo and colleagues[17] investigated the effects of hydrochloric acid and porcine pepsin solutions on canine oesophagus for periods of 3–8 h. They demonstrated that pepsin solutions of $\text{pH} < 2$ caused more severe oesophagitis than those with pH >2. Perfusion studies using a rabbit model have revealed that oesophageal mucosal injury was minimal when the perfusate contained acid alone but severe when pepsin was added[18]. In a more recent study with rabbits, Zaninotto *et al.*[19] concluded that acid–peptic injury to the oesophagus was maximal between pH 1·5 and 2·5. Although there was enzymatic activity of pepsin at pH 3, the damage to the oesophageal mucosa was greatly reduced compared with injury observed after exposure to pH 2·5. In the present study, severe mucosal injury was observed at pH 1 and 2 with no detectable change following the addition of pepsin. The injury caused by acid alone was so severe that it may have masked the synergistic effect of pepsin. At pH 3, there was a sharp decline in injury which was somewhat augmented by the addition of pepsin, although not to a significant level. There was no mucosal injury observed at pH 4 with or without pepsin.

Although a high concentration of acid alone may cause oesophagitis, animal studies have suggested that the mechanism of acid injury occurs *parri passu* with activation of pepsin[8,18,19]. Most of the above studies were done in a rabbit model which has an oesophageal epithelium covered by a thick keratin layer (not present in humans), making it difficult to evaluate the histological criteria (segmented leucocytes and reactive epithelial hyperplasia). In contrast the present experiments were performed in a feline model which is a well defined experimental model of acute oesophagitis, frequently used in previous work from the authors' laboratory[9,10,20,21]. The structural layers of the feline oesophagus not only resemble those of humans but also the histological abnormalities of the induced oesophagitis mirror those seen in routine pathology (human) specimens. Previous studies have shown that the cat oesophagus provides an ideal, reproducible and semiquantitative system for studying the biology of oesophagitis.

Prolonged oesophageal monitoring has emerged as the 'gold standard' for the detection of gastro-oesophageal reflux, which is defined as any drop in oesophageal pH below 4. The value of pH <4 has been developed on the basis of previous studies[22,23] which evaluated the effect of acid on the distal oesophagus. The present study has demonstrated that there is no morphological injury at pH 4 and suggests that pH thresholds lower than 3 should be investigated (using the current computerized pH data loggers) in the evaluation of GORD. The likelihood of oesophagitis might be better assessed by detecting oesophageal exposure time at pH <3. In summary, injury to the oesophagus is related to the pH of refluxate and is independent of the presence of pepsin. Acid–peptic injury to the oesophagus occurs at a critical threshold of acid burden (pH <3) as opposed to a graded level of injury based on a pH scale.

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Association between restriction fragment length polymorphism of the L-*myc* gene and susceptibility to gastric cancer

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Background L-*myc* polymorphism has been documented to be a representative genetic trait which is related an individual's susceptibility to several cancers. However, there have been no reports concerning any significant association between susceptibility to gastric cancer and L-*myc* polymorphism.

Methods The distribution of L-*myc* polymorphism in 61 patients with gastric cancer was determined by polymerase chain reaction-based restriction fragment length polymorphism and compared with that of 107 healthy control subjects.

Results There was a significant difference in the distribution of both genotypes ($P = 0·024$) and allele frequencies ($P = 0·026$) between the two groups. The relative risk of gastric cancer for genotypes with the shorter (S) allele was 3·09 compared with the longer (L) allele homozygote. No significant correlation with clinicopathological features of the cancers except for prognosis was found. The patients with SS genotypes had a worse prognosis than those with LL or LS genotypes ($P = 0·029$).

Conclusion L-*myc* polymorphism may be significant in an individual's susceptibility to gastric cancer in Japan, and may be a useful marker for identifying patients at high risk of developing gastric cancer.

In an effort to find a suitable genetic marker that may allow the detection of a predisposition to the initiation or progression of cancer, restriction fragment length polymorphism (RFLP) of the L-*myc* gene has been investigated in various types of cancer[1–15].

The L-*myc* gene is known to have an EcoRI restriction site at nucleotide position 2886 in intron 2; EcoRI digestion produces two types of allele, the longer (L) allele and the shorter (S) allele, with three genotypes (LL, LS and SS). Previous studies have reported that patients showing either the homozygous S-band (S–S) or the heterozygous S- and L-band (L–S) suffered a much higher incidence of metastasis and a poor prognosis for several cancers[1–2,4,6,12,14]. Two studies have tried to relate L-*myc* polymorphism to gastric carcinogenesis, but reported that there was no association between L-*myc* polymorphism and susceptibility to gastric cancer[5,12]. There was a correlation between susceptibility to metastasis and L-*myc* genotypes containing the S allele[12], but the association of L-*myc* polymorphism with susceptibility to cancer and prognosis remains unsettled.

Recent progress in molecular biological techniques has brought new tools to clinicians[16–20]. A simple and rapid genotyping method using polymerase chain reaction (PCR)-based RFLP has recently been developed which permits discrimination of the three genotypes according to the combination of their alleles. In the present study, this method was used to analyse the distribution of L-*myc* polymorphism both in patients with gastric cancer and in a large group of healthy Japanese individuals in an attempt to resolve the debate as to whether any relationship exists between polymorphism and the risk of developing this neoplasm.

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Patients and methods

Subjects

These studies were performed in 61 randomly selected patients with gastric cancer resected in 1994 and 1995, and in 107 healthy control volunteers matched for age, sex and ethnic origin with the patient group, and with no history of inbreeding and specific exposure to carcinogens. The volunteers had no symptoms and had been diagnosed to be healthy by regular medical examination such as haematological examination, chest radiography, ultrasonography and gastrofibrescopy. Informed consent was obtained from all participants.

*Determination of the L-*myc* genotype*

Genomic DNA was extracted from normal gastric mucosa of the patients with gastric cancer and from the peripheral blood of healthy volunteers. Approximately 100 ng DNA from each sample was amplified by the PCR. The PCR solution included a 10× PCR buffer (Tris hydrochloride, pH 8·3, 100 mmol/l, potassium chloride 500 mmol/l, magnesium chloride 15 mmol/l, 1 per cent Triton X-100), 2′-deoxyribonucleoside 5′-triphosphate 2·5 mmol/l (a mixture of 2′-deoxyadenosine 5′-triphosphate, 2′-deoxycytidine 5′-triphosphate, 2′-deoxyguanosine 5′-triphosphate and 2′-deoxythymidine 5′-triphosphate, each 10 mmol/l), 1·0 µmol/l of each L-*myc* primer and 1 unit Taq DNA polymerase (Promega, Madison, Wisconsin, USA). The upstream and downstream oligonucleotide primers used for amplification were 5′-ACGGCTGGTGGAGTGGTAGA-3′ and 5′-AAGCTTGAGCCCCTTTGTCA-3′ respectively, which were specifically synthesized to amplify part of intron 2. The conditions for the PCR were: 30 cycles for denaturation at 94°C for 1 min, annealing at 54°C for 2 min and extension at 72°C for 2 min. The PCR product exhibited a 613-base pair fragment. The amplified DNAs were all digested with 5 units EcoRI at 37°C for 1 h. The digested DNA fragments were separated by gel electrophoresis on 2 per cent agarose, and the responsible L-*myc* RFLP alleles were identified in each sample. The genotypes were classified into three types according to the combination of L-*myc* alleles as follows: a homozygote of L alleles which had no EcoRI restriction site, a homozygote of S alleles which had an EcoRI restriction site, and a heterozygote of L and S alleles.

Statistical analysis

The significance of variations in the L-*myc* genotypes and allele frequencies between the patients and control subjects was determined using the χ^2 test for all subjects. Furthermore, another analysis was performed after subdividing the patients with gastric cancer according to clinicopathological factors using the χ^2 test. $P < 0\cdot05$ was considered to be significant in all analyses.

Results

The pattern of EcoRI digestion for L-*myc* fragments (alleles) is shown; there were three genotypes (*Fig. 1*).

The distribution of L-*myc* genotypes found in the patients with gastric cancer and normal controls is given in *Table 1*. The distribution of each genotype in the two populations closely fits the Hardy–Weinberg equilibrium. There was a statistically significant difference in the distribution of the genotypes between the patients and control subjects ($\chi^2 = 7\cdot44$, 2 d.f., $P = 0\cdot024$), and thus there was a significant increase in the frequency of genotypes composed of the S allele in the gastric cancer population compared with the frequency in the normal population ($\chi^2 = 6\cdot25$, 1 d.f., $P = 0\cdot012$) (*Table 2*). The relative risk (odds ratio) of gastric cancer for those with the LS plus SS genotypes compared with the LL genotype was 3·09 (95 per cent confidence interval 1·33–7·21) (*Table 2*).

No significant difference was found when the patients with gastric cancer were subdivided according to clinicopathological factors such as histology, depth of invasion, lymphatic permeation, vascular permeation, lymph node metastasis and clinical stage (*Table 3*). Eighteen (30 per cent) of 61 patients and 33 (30·8 per cent) of 107 volunteers were smokers. There was no association between smoker or non-smoker status and L-*myc* allele distribution. Seven of 46 patients with LL or LS genotypes died from recurrent disease, while seven of 15 patients with an SS genotype died from recurrent disease. There was a significant difference between L-*myc* alleles and prognosis ($P = 0\cdot029$).

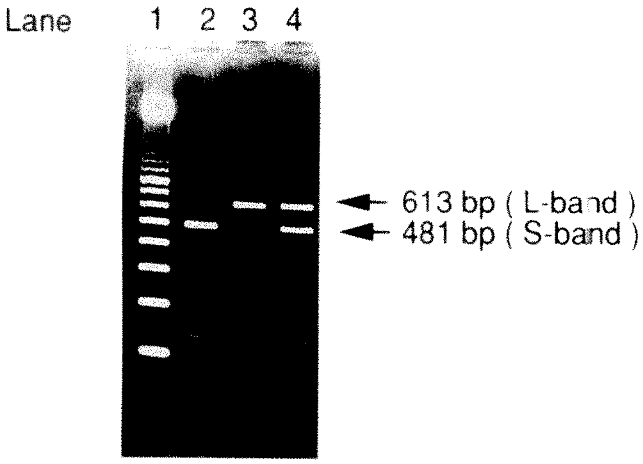

Fig. 1 Digestion pattern of L-*myc*. Amplified DNA fragments were digested with EcoRI, then applied to a 2 per cent agarose gel containing ethidium bromide. Lane 1, 100-base pair (bp) ladder used as a molecular marker; lane 2, DNA from the homozygote for the shorter (S) allele (481 bp), showing complete digestion with EcoRI; lane 3, DNA from the homozygote for the longer (L) allele (613 bp), lacking the EcoRI site; and lane 4, DNA from the heterozygote for the S and L allele. The other digested fragment of S allele (132 bp) was seen as a ghost band (lanes 2 and 4)

Table 1 Distribution of L-*myc* restriction fragment length polymorphism genotypes in patients with gastric cancer and healthy subjects

		No. with genotype		
	n	SS	LS	LL
Patients	61	15 (25)	38 (62)	8 (13)
Controls	107	18 (16·8)	55 (51·4)	34 (31·8)

Values in parentheses are percentages. L-*myc* genotypes have shorter (S) and/or longer (L) alleles. $P = 0\cdot024$ (2d.f., χ^2 test)

Table 2 Distribution of L-*myc* restriction fragment length polymorphism genotypes in patients with gastric cancer and healthy subjects

		No. with genotype	
	n	SS + LS	LL
Patients	61	53 (87)	8 (13)
Controls	107	73 (68·2)	34 (31·8)

Values in parentheses are percentages. L-*myc* genotypes have shorter (S) and/or longer (L) alleles. There was a significant difference in the distribution of genotypes (SS plus LS *versus* LL) between patients and controls ($P = 0\cdot012$, 1 d.f., χ^2 test). The relative risk of gastric cancer for genotypes with the S allele (SS plus LS) compared with the LL genotype was 3·09 (95 per cent confidence interval 1·33–7·21)

Table 3 Distribution of L-*myc* genotypes in patients with gastric cancer subdivided according to clinocopathological factors

Variable	No. of subjects*	L-*myc* genotype LL	LS	SS	*P*
Histology					
Differentiated	28	4	15	9	0·51
Undifferentiated	22	3	15	4	
Depth of invasion					
No serosal invasion	32	3	22	7	0·65
With serosal invasion	26	4	15	7	
Lymphatic permeation					
Positive	20	3	13	4	0·80
Negative	38	4	24	10	
Vascular permeation					
Positive	41	4	26	11	0·59
Negative	17	3	11	3	
Lymph node metastasis					
Positive	24	4	16	4	0·42
Negative	34	3	21	10	
Clinical stage					
I and II	36	4	23	9	0·86
III and IV	20	3	13	4	

L-*myc* genotypes have shorter (S) and/or longer (L) alleles. *Patients showing indistinct data in each category were excluded

The frequency of the S allele was greater than that of the L allele in the patient group (0·56 *versus* 0·44), in contrast to 0·43 *versus* 0·57 in the normal control group ($\chi^2 = 4{\cdot}93$, $P = 0{\cdot}026$). The relative risk of gastric cancer for those with the S allele compared with the L allele was 1·70 (95 per cent confidence interval 1·23–4·13).

Discussion

The L-*myc* gene was isolated initially on the basis of its high level of amplification in a subset of human small-cell lung cancers, and it is thought to be a nuclear oncogene activated late in tumorigenesis[21,22]. Since a study of L-*myc* RFLP in Japanese patients with lung cancer was first reported in 1988[1], many investigators have analysed the L-*myc* RFLP types in patients with lung cancer[4,7,9,15] and other malignant tumours, such as renal cancer[2], gastric cancer[5,12], bone or soft tissue sarcomas[11], oral cancer[6], colorectal cancer[3,10], breast cancer[12] and hepatocellular carcinoma[8]. It remains controversial as to whether L-*myc* polymorphism may affect susceptibility to tumour. Although Kato *et al.*[11] reported an association between SS genotype and susceptibility to bone and soft tissue sarcoma in male patients, no such association was found with the incidences of lymphoma and leukaemia[13] and breast cancer[14]. In contrast, Taylor *et al.*[8] showed a protective effect of the SS genotype in hepatocellular carcinoma.

There was a significant difference in the distribution of L-*myc* RFLPs between patients with gastric cancer and healthy Japanese subjects in the present study. This positive finding persisted when the patients were classified into two genotypes, 'LS plus SS' and 'LL' types, or when they were analysed according to allele frequency. Therefore, it is concluded that, at least for Japanese patients, the polymorphism of L-*myc*, especially in individuals having the S allele, may play a significant role in the genetic susceptibility to gastric cancer. These findings are incompatible with two previous studies of gastric cancer[5,12]. The distribution of genotypes or allele frequency in the present control population was statistically similar to that in Australians[13], Indians[6], Norwegians[9] and white Caucasians[5,7], and to that reported in the Japanese population[11], but not to that reported by Ishizaki *et al.*[12]. Several reports on lung cancer are also inconsistent[7,9]. A possible explanation for these contradictory results may be that they are due to differences in environmental factors or in the ethnic origins of the population analysed. The cancer incidence of many tumour types, if not all, will also vary because of both environmental and genetic factors. Further studies on the allele distribution in relation to ethnic differences are required to clarify the genetic susceptibility to cancer, such as in black Americans who show a higher frequency of the SS genotype of L-*myc*[7].

The reason why polymorphism of the L-*myc* gene is related to genetic susceptibility to gastric cancer is unknown. It is possible that a gene or genes that are closely associated with L-*myc* on the same chromosome are related. Interestingly, it was observed recently that the L-*myc* genotype was associated with a significantly higher level of allele loss from chromosomal arms[10]. Consequently it may be that L-*myc* polymorphism might not influence biological behaviour of a tumour except as a marker in linkage disequilibrium with an as yet unknown susceptibility gene. On the other hand, it is of course possible that the L-*myc* oncogene itself is directly involved.

Although the L-*myc* genotype has consistently been analysed using Southern blotting in previous studies, this study utilized a molecular genotyping method involving PCR–RFLP. As the epidemiological risk factors for gastric cancer involve individual acquired conditions such as smoking, alcohol intake and gastritis[23], this method should be applicable to individuals at high risk in an attempt to select such individuals more objectively. Testing several genetic polymorphisms simultaneously has the potential to identify individuals with an extremely high risk of developing cancer. This has profound implications for prevention since such high-risk individuals may be screened intensively as well as potentially treated with several preventive approaches. From a clinical viewpoint, this method appears to be an accurate and reliable approach for the mass screening of a large number of patients, because it can be performed rapidly and simply by examining only a small amount of genomic DNA isolated from peripheral blood or a buccal smear. L-*myc* RFLP analysis may therefore be a useful marker for predicting a higher risk for gastric cancer, at least in the Japanese population.

Some studies have suggested that the presence of the S allele was associated with a poor prognosis because of metastasis. Since a close correlation between the S allele and an individual's predisposition to metastasis, especially to lymph nodes and distal organs, was reported in lung cancer[1], similar associations have been shown in renal[2], cancer[6], gastric[12] and breast[14] cancer. The present study disclosed similar results, that patients with the S–S alleles showed a worse prognosis than those with L–L or L–S types. In contrast, no correlation between L-*myc* RFLP and metastasis has been reported in colorectal[3], breast[12] or lung[7,9] cancer.

Acknowledgements

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Surgical Research Society Abstracts

The following abstracts were presented at the 87th meeting of the Surgical Research Society. The meeting was organized by the Academic Department of Surgery, United Medical and Dental School, Guy's and St Thomas', and held on 8–9 January 1988 at Guy's and St Thomas' Hospital, London, UK. Ninety-seven papers were presented during the scientific sessions. The Patey Prize was awarded to Dr R. L. Loveday for her paper entitled 'Genetic analysis of breast tumours by comparative genomic hybridization'.

Monocyte chemotactic protein 1 accelerates thrombus resolution

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Background Monocyte infiltration into venous thrombi increases with time and this is associated with raised plasminogen activator levels. Monocyte chemotactic protein 1 (MCP-1) is chemotactic for monocytes. It was hypothesized that administration of MCP-1 might increase monocyte recruitment by the thrombus and enhance its resolution.

Methods Home Office approval was obtained for a rat model of thrombosis to be used in two experiments. (1) Two cohorts of five animals received 1 μg recombinant rat MCP-1 or its carrier. Specimens were harvested at 1 week and paraffin sections were stained with Martius Scarlet Blue and a rat monocyte marker (clone ED-1). Slides were scored blindly by three independent observers for macrophage, erythrocyte, collagen, fibrin and smooth muscle cell content, lumen size and degree of recanalization. (2) Thrombi from control and test cohorts were weighed at 7 and 10 days ($n = 22$).

Results (1) Organization scores were found to be significantly higher in the MCP-1 group (control median 29, test median 59; $P < 0{\cdot}0005$). There was no significant interobserver difference in scores. (2) Thrombus weights in the MCP-treated group were significantly greater than those in the control group ($P = 0{\cdot}02$). Thrombus weights in the control group were higher at 10 than 7 days whereas in the MCP group, thrombus weights were lower at 10 days than at 7 days.

Conclusion (1) Infusion of MCP-1 accelerates thrombus maturity. (2) It is known from models of thrombosis that after induction, thrombus increases in weight for a number of days before resolving. It is possible that the thrombus weight–time curve may have been shifted to the left by MCP-1 administration. Early organization may be beneficial in resolving human thrombi making MCP-1 of potential therapeutic use.

Calcium antagonists accelerate elastin destruction in a model of aneurysmal disease

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Background Abdominal aortic aneurysms (AAAs) are characterized by changes in the extracellular matrix of the arterial media, in particular a reduction in elastin concentration. These changes are mediated by increased levels of endogenous matrix metalloproteinases (MMPs). MMP activity is influenced by a number of therapeutic agents and recently calcium channel blockers have been shown to increase the proteolytic activity of MMP-2 secreted by vascular smooth muscle cells. It may therefore be hypothesized that calcium antagonists may potentiate the activity of MMPs in aneurysmal disease and thus accelerate AAA expansion. In this study, the ability of amlodipine to influence elastin degradation, was assessed in a previously described model of aneurysmal disease.

Methods Porcine aortic segments ($n = 8$) were preincubated in exogenous pancreatic elastase for 24 h before culture in standard conditions for 6 days with amlodipine 10 and 100 $\mu g\,l^{-1}$. Control segments were cultured both without amlodipine and without elastase. At the termination of culture MMPs were extracted from the tissue and quantified by a combination of substrate gel enzymography and immunoblotting. The volume fractions of elastin and collagen were determined by stereological analysis of elastic Van Gieson-stained sections.

Results Gel enzymography demonstrated significantly increased MMP-9 activity in the amlodipine-treated segments and this raised activity was reflected in a significant destruction of medial elastin.

Aorta	Elastin (%)	MMP-9 (units)
Cultured control	54·2 (45·4–62·2)	2·86 (2·55–3·17)
Elastase	40·5 (27·2–48·8)	2·81 (2·60–3·71)
Elastase/amlodipine 10 $\mu g\,l^{-1}$	33·6 (27·9–40·8)	4·22 (3·98–4·86)†
Elastase/amlodipine 100 $\mu g\,l^{-1}$	27·0 (18·5–38·2)*	4·18 (3·93–5·07)‡

Values in parentheses are interquartile ranges. $^*P < 0{\cdot}05$, $^†P < 0{\cdot}01$, $^‡P < 0{\cdot}02$

Conclusion Therapeutic ranges of amlodipine significantly enhanced elastin degradation and potentiated MMP-9 activity within the aortic organ cultures. These data suggest that amlodipine may accelerate AAA growth.

Oral eicosapentaenoic acid reduces experimental human pancreatic tumour growth in mice with severe combined immunodeficiency

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Background The authors have recently shown that eicosapentaenoic acid (EPA), a fatty acid derived from fish oil, will attenuate cachexia in patients with advanced pancreatic cancer. Others have suggested that EPA will slow experimental tumour growth in mice but most have used mixed fish oil preparations or administered the agent by non-physiological routes. This study aimed to assess the effect of dietary high-purity EPA upon the growth of a human pancreatic cancer cell line in immunocompromised mice.

Methods Fragments of tumour derived from the MIAPaCa-2 human pancreatic cancer cell line were transplanted subcutaneously in 5–6-week-old female mice with severe combined immunodeficiency after Home Office approval. From the day after tumour implantation mice were fed a purified fat-free diet to which was added oil to make up 5 per cent of the final diet weight, using either corn oil or 95 per cent pure EPA as free acid (4 per cent, plus 1 per cent corn oil). Mice were killed before the tumour burden became excessive at around 3 weeks.

Results Mice fed the diet enriched with EPA had significantly smaller tumours than control animals (median 2810 *versus* 4960 mm^3; $P = 0{\cdot}023$, Mann–Whitney U test). Liver and spleen were the main site of metastases and these organs were significantly lighter in EPA-fed animals than those fed corn oil

($P<0\cdot001$) suggesting a reduced metastatic burden. Mice fed EPA ate significantly less food than controls (2·25 *versus* 3·05 g day^{-1}, $P=0\cdot021$). As diet restriction has been suggested to inhibit carcinogenesis the experiment was repeated but matched amounts of food were supplied. Again tumours were significantly smaller (3080 *versus* 4800 mm^3, $P=0\cdot027$) and liver and spleens were significantly lighter ($P<0\cdot02$) with EPA.

Conclusion It is concluded that EPA 6–8 g kg^{-1} within the diet will slow experimental tumour growth and metastatic spread in mice.

Claudication grade: effect on total antioxidant capacity and systemic vascular permeability

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Background The leucocyte has been implicated as a mediator of ongoing vascular damage in patients with peripheral vascular disease (PVD). The chronic consequences of PVD may therefore be reflected by systemic changes in total antioxidant capacity and vascular permeability commensurate with increasing severity of PVD. The aim of the study was to assess if increasing grade of PVD, according to Society for Vascular Surgery/International Society for Cardiovascular Surgery classification influences total antioxidant defences and systemic vascular permeability.

Methods Data were collected from 25 patients with grade 2 claudication (ankle to brachial pressure index (ABPI) 0·1(0–0·2)), 28 patients with grade 1 claudication (ABPI 0·8(0·6–0·8)), and 22 patients with grade 0 claudication (controls) (ABPI 1·2(1·1–1·3)). Patient demographics were matched. Total antioxidant capacity (TAC), urine albumin to creatinine ratio (UACR) and neutrophil CD11b expression were determined from resting samples collected in the morning.

Results There was no significant difference in TAC between the three groups. Grade 2 claudicants had significantly higher urine albumin leak ($P<0\cdot01$), and CD11b expression ($P<0\cdot01$), compared with the control group and grade 1 claudicants.

Category of PVD	No.	TAC	Neutrophil CD11b (m.c.f.)	UACR (mg mmol^{-1})
Grade 0	22	720 (630–858)	2·5 (2·2–3·2)	0·5 (0–1·3)
Grade 1	28	813 (636–909)	3·1 (2·4–3·9)*	2·0 (0·9–3)*
Grade 2	25	765 (400–980)	11·5 (7·3–15·2)†	6·4 (1–7·5)†

Values are median (i.q.r.). m.c.f., mean channel fluorescence. *$P<0\cdot05$, †$P<0\cdot01$ *versus* control group (Mann–Whitney *U* test)

Conclusion This study, for the first time provides evidence of the systemic changes associated with increasing severity of PVD. Although there is an increase in resting neutrophil activation and endothelial damage with increasing severity of PVD this is not balanced by changes in total antioxidant defences.

Long-term renal transplant function is predicted by interstitial staining for collagen III in 6-month protocol biopsies

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Background Chronic transplant rejection has emerged as the commonest cause of long-term renal allograft failure. Early identification of those grafts at risk could allow targeting of specific therapies aimed at delaying this process.

Methods A consecutive series of 48 renal transplant recipients with 5-year follow-up data were studied. All patients underwent protocol needle-core transplant biopsies at 1, 3 and 6 months after operation. All patients were immunosuppressed with cyclosporin and prednisolone (with or without azathioprine). In this study the 6-month protocol biopsies were analysed by computerized histomorphometry. No patient had clinical rejection at the time of the biopsy. Immunostaining for collagen III, tenascin and infiltrating leucocytes was performed using an indirect immunoperoxidase technique. Interstitial area stained (%) was measured by a blinded research associate using a semi-automatic image analysis system. Images from biopsy sections were transferred in digital form by a microscope-mounted video camera to a microcomputer fitted with a frame grabber card. The area fraction occupied by the substance under study was computed using the program NIH Image on non-counterstained sections. The results were related to glomerular filtration rates measured at 6, 12 and 24 months after transplant using rank correlation coefficients.

Results Six-month glomerular filtration rate correlated with percentage area of collagen III ($r=0\cdot42$, $P=0\cdot005$), tenascin ($r=-0\cdot41$, $P=0\cdot007$) and leucocytes ($r=-0\cdot36$, $P=0\cdot02$). Furthermore, a percentage area of collagen III of more than 40 per cent at 6 months was associated with a significantly lower GFR at 24 months than a percentage area of 40 per cent or less (mean(s.d.) 30·8(3·6) *versus* 44·8(3·6) ml per min per 1·73 m^2, $P=0\cdot01$). Donor age correlated with collagen III and tenascin staining at 6 months ($r=0\cdot33$, $P=0\cdot03$) but not with leucocyte staining, and was also predictive of long-term graft outcome.

Conclusion Grafts with poor long-term function can be predicted using early (6 month) protocol biopsies immunostained for collagen III, tenascin and leucocytes. The predictive graft changes at this time may reflect donor characteristics rather than those arising *de novo* in the recipient.

Local or general anaesthesia for carotid endarterectomy: a formal trial is overdue

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Background Although carotid endarterectomy (CEA) performed under local anaesthesia (LA) allows optimum cerebral monitoring and maintains cerebral autoregulation it is suggested that hypertension and catecholamine release increase cardiac morbidity. However a recent meta-analysis of non-randomized studies (2070 LA, 3447 general anaesthesia (GA)) suggests that death (0·8 *versus* 1·2 per cent), stroke (2·0 *versus* 5·3 per cent) and myocardial infarction (MI) (0·6 *versus* 1·3 per cent) are less frequent in patients who have LA.

Methods In a prospective study 89 CEAs were performed under LA (superficial and deep cervical plexus block; 20 ml 0·5 per cent bupivacaine, 20 ml 1 per cent prilocaine) and 101 under GA (1 mg alfentanil, 0·5–2·0 per cent isoflurane, nitrous oxide/oxygen). Although non-randomized, patients had a free choice as to the type of anaesthetic. The sex ratio (LA M:F 65:24, GA 57:44), mean age (67·9 *versus* 68·1 years) and history of ischaemic heart disease (31 *versus* 34 per cent), hypertension (66 *versus* 56 per cent), smoking (52 *versus* 64 per cent) and diabetes (11 *versus* 14 per cent), confirmed that the two groups were similar as did the indications for surgery (LA *versus* GA): transient ischaemic attack (38 *versus* 38 per cent), cerebrovascular accident (CVA) (33 *versus* 32 per cent), amaurosis (23 *versus* 25 per cent), asymptomatic (6 *versus* 5 per cent) and the presence of greater than 70 per cent bilateral stenoses (37 *versus* 35 per cent).

Results The outcome of CEA is shown in the *Table*.

	LA	GA
n	89	101
Shunted	15 (17)	67 (66·3)
Stump pressure < 50 mmHg	46 (52)	67 (66·3)
30-day stroke rate	0	4 (4·0)
Perioperative MI	1 (1)	3 (3·0)
Death	1 (1)	2 (2·0)

Values in parentheses are percentages. $P = 0{\cdot}057$ (30-day CVA rate); $P = 0{\cdot}046$ (combined MI/CVA)

Conclusion These results support the concept that all complications of CEA may be less frequent when surgery is performed under LA and reinforce the need for a prospective randomized trial.

Polymorphisms within the tumour necrosis factor region affect survival of patients with oesophageal cancer

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Background Genetically, the control of tumour necrosis factor (TNF) α production has been associated with a number of polymorphic sites present near the TNF locus in the class III region of the major histocompatibility complex (MHC). This study examines the TNFB locus, which has previously been shown to influence the TNF-α production both *in vitro* and *in vivo* in patients with oesophageal cancer and investigates if correlations exist between cytokine production and clinical outcome.
Methods Genomic DNA was isolated from the peripheral blood of 46 patients with cancer and 47 controls. Using polymerase chain reaction, a 782 base-pair fragment containing the TNFB locus was amplified and subjected to NcoI restriction analysis to detect which TNFB allele was present.
Results Both the cancer and control groups had similar TNFB allelic frequencies. In the cancer group, 6 per cent were homozygous for TNFB1 (associated with low TNF-α production), 57 per cent were heterozygotes (TNFB1, 2) and 37 per cent homozygous for TNFB2 (associated with high TNF-α production). Significant correlations were made between survival and TNFB status, with 0, 49 and 82 per cent of patients with TNFB1, 1 ($n = 3$), TNFB1, 2 ($n = 26$) and TNFB2, 2 ($n = 17$) alleles respectively surviving their first year ($P < 0{\cdot}004$).
Conclusion While there is overproduction of TNF-α in patients with oesophageal cancer, this seems to be inversely associated with the allele TNFB1 which underexpresses TNF-α. This implies that some other polymorphic site may be associated with increased TNF-α production in these patients. TNFB status is prognostic in predicting poor patient survival and this may be due to linkage with other loci within the TNF or MHC regions. These studies indicate that genetic predisposition may direct the inflammatory response in cancer patients and may have prognostic significance.

K-*ras* mutation and 8p12 deletions both occur frequently in early colorectal tumours

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Background Mutational analysis of colorectal cancers suggests that different genetic changes can produce tumours with distinct clinicopathological features. Chromosome 8p has been implicated in deletional studies. K-*ras* mutations occur with higher frequency in early tumours. K-*ras* activation has been studied in combination with deletions at 8p12.
Methods Eleven adenomas and 70 consecutive colorectal cancers including seven $T_1 N_0 M_0$ tumours, were genotyped from tumour extracted DNA. K-*ras* mutations were examined by the amplification refractory mutation scheme test; interstitial deletions on 8p12 were identified using polymorphic microsatellite markers (DS8-87, -505, -513, -259, -278).
Results Seven adenomas had K-*ras* mutations, three of which also had allelic loss at 8p12. Four of seven T_1 tumours had isolated 8p12 deletions compared with two of 63 advanced tumours ($P = 0{\cdot}0005$). K-*ras* mutations were seen in four of seven T_1 tumours and 15 of 63 advanced tumours ($P = 0{\cdot}08$). Both mutations occurred in three of four T_1 carcinomas. This relationship was not seen in the advanced tumours ($P = 0{\cdot}02$). Absence of both changes was found in only one T_1 lesion and in 47 advanced tumours ($P = 0{\cdot}02$).
Conclusion These findings show a clear predilection of these two changes for early tumours, and these events tend to occur in the same tumours. This suggests multiple genetic pathways for colorectal cancer, and may indicate that certain pathways will result in neoplasms with a less aggressive phenotype.

Serum vascular endothelial growth factor in breast cancer

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Background Vascular endothelial growth factor (VEGF) is one of the most potent angiogenic cytokines. Its intratumoral levels correlate with microvessel density, nodal metastasis and disease-free survival. This study evaluates the relation between serum VEGF and various pathological indices of breast cancer.
Methods Serum VEGF 165 was assayed before operation in 135 patients with breast malignancies and compared with serum VEGF levels in 72 healthy female controls. All tumours were staged by a single pathologist according to the tumour node metastasis classification.
Results Serum VEGF was raised in all stages of breast cancer. Levels in nodal, recurrent and metastatic disease were significantly higher than those in controls. Patients with ductal carcinoma *in situ* (DCIS) had raised levels compared with controls. Some 67 per cent of patients had raised VEGF levels compared with 11 per cent with raised CA15-3 and 13 per cent with abnormal carcinoembryonic antigen levels.

	VEGF (pg ml^{-1})	P*
Controls ($n = 72$)	173·8 (92·5–252·5)	
DCIS ($n = 8$)	450·4 (301·8–795·2)	0·002
Ductal carcinoma ($n = 95$)	307·7 (155·5–483·0)	< 0·0005
Lobular carcinoma ($n = 16$)	207·1 (118·7–379·8)	0·32
ER positive ($n = 62$)	305·9 (179·7–485·2)	< 0·0005
ER negative ($n = 20$)	267·8 (94·2–523·7)	0·1

Values are median (interquartile range). ER, oestrogen receptor. *Mann–Whitney *U* test

VEGF levels were not significantly raised in patients with lobular cancer or those with ER-negative tumours.
Conclusion Serum VEGF shows a correlation not only with tumour stage and cancer cell type but also with ER status. This may have implications in the study of hormones in the aetiology, pathogenesis and prognosis of breast cancer. As serum VEGF is more sensitive than currently employed tumour markers, it may have a role in monitoring disease prognosis in patients with breast cancer.

Positron emission tomography in assessing axillary lymph node status in breast cancer

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Background The single most important prognostic factor in breast cancer is axillary node involvement by tumour. Assessment of nodal status requires axillary dissection resulting in additional time in hospital and postoperative morbidity. A reliable non-invasive method of determining axillary node status would be valuable. Positron emission tomography (PET) produces images based on the distribution and metabolism of administered positron-emitting compounds, reflecting functional rather than anatomical characteristics of the imaged tissue. PET, therefore, may allow identification of metastatic tumour in regional lymph nodes. The role of PET was assessed in staging the axilla in breast cancer.
Methods Patients with untreated breast cancer underwent PET, using between 105 and 185 Mbq 2-deoxy-2-(F18) fluoro-D-glucose, of the axillae and upper thorax before surgery. Patients were examined clinically following PET. The accuracy of clinical and PET node staging was compared with node histology following surgical excision.
Results Some 50 patients underwent PET imaging. Twenty-one had involved axillary nodes at histology; PET demonstrated 19 involved nodes. Twenty-nine patients did not have any nodes involved at histology; PET showed involvement in one and none in 28. Therefore, PET had a specificity of 97 per cent and a sensitivity of 90 per cent (accuracy 94 per cent). Clinical examination had a specificity of 90 per cent and a sensitivity of 57 per cent .
Conclusion PET has a high sensitivity and specificity for detecting axillary node involvement in breast cancer. Its use in staging of breast cancer may obviate the need for axillary surgery in many patients.

Antioestrogen therapy does not affect cell death or cell proliferation in comedo ductal carcinoma *in situ* of the breast

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Background Over 50 per cent of screen-detected ductal carcinoma *in situ* (DCIS) lesions are of the comedo subtype which are usually oestrogen independent. The value of antioestrogen therapy in preventing recurrence of DCIS following breast conserving surgery is currently under evaluation.
Methods Using an *in vivo* model for human DCIS the effect of antioestrogen treatment on programmed cell death (apoptosis) and cellular proliferation (Ki67 immunoreactivity) in DCIS lesions was examined. In each experiment, athymic nude mice (median no. 16 (range 12–20)) were implanted with eight DCIS xenografts per mouse and given either no treatment or weekly injection of 0·1 ml Faslodex (a pure antioestrogen) for 2 weeks. Xenografts were then removed and apoptotic and Ki67 indices compared between treatment groups by examining cell morphology on sections stained with haematoxylin and eosin (no. of cells exhibiting apoptosis/total no. of cells counted) or by immunohistochemistry (Ki67 proliferation index).
Results All non-comedo lesions and three of 15 comedo DCIS lesions were oestrogen receptor (ER) positive. Pretreatment apoptotic and proliferative rates were significantly higher in comedo than non-comedo lesions ($P < 0·0001$ and $P = 0·02$ respectively, Mann–Whitney U test).

	Comedo DCIS ($n = 15$)		Non-comedo DCIS ($n = 5$)	
	Apoptotic index (%)	Ki67 index (%)	Apoptotic index (%)	Ki67 index (%)
Pretreatment	1·6 (0·7–3·7)	16·2 (7–46)	0·4 (0·1–0·6)	2·2 (0–16)
Control group	1·4 (0–3·5)	16·9 (2–29)	0·4 (0·1–1·7)	7·0 (2–21)
Antioestrogen group	0·8 (0·4–3·6)	14·8 (14–18)	1·0 (0·5–2·0)	8·1 (4–11)
P*	n.s.	n.s.	0·04	n.s.

Values are median (range). n.s., Not significant. *Mann–Whitney U test

Following antioestrogen treatment, non-comedo DCIS (usually ER positive) displayed increased apoptotic cell death compared with controls whereas comedo DCIS (usually ER negative) was unresponsive.
Conclusion Women with comedo DCIS are unlikely to benefit from antioestrogen therapy and other therapeutic strategies need to be investigated.

Accuracy of one-stop diagnosis for 1110 patients presenting to a symptomatic breast clinic

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Background To minimize delay and anxiety and reduce unnecessary open biopsies, triple assessment with immediate reporting has been used in this symptomatic breast clinic since 1991. The effectiveness and reliability of the process requires careful evaluation. The aim of this study was to establish the accuracy of the diagnostic modalities used and the efficacy of this one-stop diagnostic policy.
Methods The data on 1110 patients, newly presenting to the symptomatic breast clinic between January and July 1993, were analysed and the subsequent 3-year follow-up and outcome established. Sensitivity, specificity and predictive values were determined using standard statistical analysis (SPSS for Windows).
Results Fine-needle aspiration cytology (FNAC) provided the highest (97·3 per cent) overall prediction of benign and malignant lesions, with a sensitivity of 93·5 per cent and specificity of 98·1 per cent. Ultrasonography provided 97·0 per cent overall prediction with a sensitivity of 88·9 per cent and specificity of 97·4 per cent. Mammography provided 96·4 overall prediction with a sensitivity of 93·2 per cent and a specificity of 96·7 per cent. When the mammogram or ultrasonographic scan were reported benign, the false-negative rate was 0 per cent. The false-positive and false-negative rates for FNAC were 2·4 and 1·4 per cent respectively. Following assessment, a diagnosis was made in 96 per cent of patients; 62 per cent were discharged at the first clinic visit.
Conclusion The one-stop symptomatic breast clinic provides a quick, accurate and effective means of establishing a diagnosis.

Desmoglein 2 expression in primary breast cancer and its relation to a series of prognostic markers

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Background Desmoglein 2 (Dsg2) is a novel calcium-dependent transmembranous glycoprotein forming a subfamily of the cadherin group of adhesion molecules. Its role as a potential metastatic suppressor molecule has been demonstrated in transitional and squamous cell carcinomas and in the authors' recent *in vitro* data. However its expression and role in breast cancer *in vivo* has yet to be established.

Methods The aim of this study was to demonstrate and establish the level of immunohistochemical (IHC) expression of Dsg2 in breast cancer specimens ($n = 68$) as well as in ductal carcinoma *in situ* (DCIS) ($n = 3$), tumour-associated normal (TAN) ($n = 11$) and normal ($n = 9$) breast tissue. Second, the IHC level of Dsg2 expression and a series of prognostic markers (oestrogen and progesterone receptors, Ki67, epidermal growth factor receptor, grade and size of tumour, lymph node involvement and menopausal status) were compared.

Results The majority of cancers (98 per cent) demonstrated membranous staining for Dsg2. However, Dsg2 expression was significantly reduced in breast cancer when compared with normal and TAN breast tissue ($P < 0{\cdot}0001$) but not with DCIS ($P = 0{\cdot}67$). A significant inverse relationship between tumour size and Dsg2 expression was demonstrated ($P = 0{\cdot}012$), but no correlation could be shown between Dsg2 level and the other prognostic markers.

Conclusion These data suggest that Dsg2 may have a potential role in local breast cancer progression, but have not provided evidence for a metastatic suppressor role for Dsg2.

Effect of antioestrogens on BRCA-1 mutated breast tissue compared with normal breast

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Background Women found to have the BRCA-1 genotype are randomized into tamoxifen *versus* placebo breast cancer prevention trials, but little is known of tamoxifen's effects on their breast tissue.

Methods The effects of tamoxifen and a pure antioestrogen (ICI 182780) were studied on breast tissue from women with known BRCA-1 mutations ($n = 3$), other 'high risk' women in whom genetic testing was not possible ($n = 10$) and normal women undergoing benign breast biopsies ($n = 6$). Tissue was implanted into the flanks of athymic nude mice ($n = 20$) and 2 weeks later treated either with slow-release oestradiol (E_2 2 mg; $n = 12$) or control pellets ($n = 8$). One week later control mice were treated with vehicle ($n = 4$), tamoxifen (1 mg day^{-1}; $n = 2$), or ICI 182780 (5 mg week^{-1}; $n = 2$) injections for 2 weeks and E_2 mice with vehicle ($n = 4$), tamoxifen (1 mg day^{-1}; $n = 4$), or ICI 182780 (5 mg week^{-1}; $n = 4$). Implants were removed for histological examination and assessment of proliferation (Ki67) using immunocytochemistry at weeks 2, 3, 4 and 5. This work has ethics committee and Home Office approval.

Results Of 1370 implants retrieved, 1008 (73·6 per cent) contained normal breast nodules. In all groups there was a significant rise in Ki67 expression after E_2. In the normal risk group, tamoxifen could reduce Ki67 to near control levels (mean(s.d.) 1·9 (1·5) *versus* 1·9 (1·9) per cent cells positive). In the 'high risk' group, tamoxifen had no significant effect on Ki67 but after ICI 182780, Ki67 fell from 3·5 (3·4) in the E_2 alone group to 1·8 (2·6) ($P = 0{\cdot}009$, Mann–Whitney U test). In the BRCA-1-mutated group Ki67 fell from 4·5 (6·3) in the E_2 alone group to 2·2 (4) after tamoxifen and 2·1 (2·7) after ICI 182780.

Conclusion The BRCA-1-mutated breast proliferates in response to oestrogen. This proliferation is abrogated by tamoxifen and ICI 182780 but the latter appears more potent.

Possible therapeutic role of short chain fatty acids in diversion colitis of the neobladder

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Background Short chain fatty acids (SCFAs), butyrate especially, are a major energy substrate for colonic mucosal cells. They are also antiproliferative differentiation inducers. Diversion colitis may be reversed by their instillation. A similar condition (and subsequent neoplasia) can occur in neobladders reconstructed using colon. Proposals to treat this with intravesical SCFAs have led to an investigation of their effects on urothelium.

Methods Wistar rats were given 0·4 ml of an SCFA cocktail (butyrate 40 mmol l^{-1}) intravesically daily for 5 days. A [14C] butyrate tracer was also used. Bladder histology was performed up to 14 days thereafter. Primary normal urothelial cells were isolated from ureter by sequential ethylenediamine tetra-acetic acid and collagenase IV treatment, and grown on for not more than five passages in a supplemented keratinocyte serum-free medium. A tetrazolium cytotoxicity assay was performed on cells seeded in 96-well plates, exposed to SFCA or control for 2–72 h, washed and grown on for 5 days.

Results Instillation of SCFAs caused no histological change. Butyrate was readily absorbed and 89 per cent of absorbed counts were sequestered in the liver 1 h after instillation. The *in vitro* reduction of biomass directly related to drug concentration and exposure time, e.g. 40 per cent ($P < 0{\cdot}01$) at 2 h and butyrate 20 mmol l^{-1}; 10 mmol l^{-1} had no effect.

Conclusion The cytostatic effect of SCFAs seen *in vitro* is not reflected in gross histology. However, there is substantial absorption through urothelium. The prospects for therapeutic use are promising.

Effect of sympathetic co-transmitters on human mesenteric arteries and veins

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Background Sympathetic perivascular nerves contain noradrenaline (NA), neuropeptide Y (NPY) and adenosine 5′-triphosphate (ATP) as co-transmitters. The effect of these transmitters on human mesenteric arteries and veins was investigated.

Methods Mesenteric vessels from patients with non-inflammatory conditions were dissected from operative specimens. Organ-bath pharmacology on ring segments was used to determine the cumulative dose–response curves for NA alone and with a subthreshold dose of NPY, NPY alone and ATP.

Results

Transmitter	Vessel	n	E_{max} (%)	EC_{50}
NA	artery	6	125·3 (9·8)†	5·23 (0·06)‡
	vein	11	64·1 (9·7)	6·07 (0·04)
NPY	artery	6	0	0
	vein	6	Variable contraction at doses $> 3 \times 10^{-8}$ mol l^{-1}	
NA + NPY 3×10^{-8} mol l^{-1}	artery	6	110·6 (2·2)	5·29 (0·02)
	vein	6	100·8 (17·8)¶	6·47 (0·04)**
ATP	artery	7	—	3·22 (0·07)*§
	vein	8	—	4·31 (0·28)*

Values are mean(s.d.). E_{max}, maximal contraction to exogenous transmitter as percentage of contraction to potassium chloride 120 mmol l^{-1}; EC_{50}, $-$log of dose giving 50 per cent maxima contraction; *p[A]$_{25}$ (dose giving 25 per cent maximal contraction to KCl 120 mmol l^{-1}). †$P < 0{\cdot}001$, ‡$P < 0{\cdot}0001$, §$P < 0{\cdot}005$ *versus* veins (two-sample t test); ¶$P < 0{\cdot}02$, **$P < 0{\cdot}001$ *versus* NA only (paired t test)

Conclusion These data suggest that both NA and ATP are involved in sympathetic neurotransmission in human mesenteric vessels. NPY in mesenteric veins modulates the effect of NA but its role in mesenteric arterial sympathetic nerves is unclear. Studies on other vessels demonstrated a greater effect of NPY on arteries than veins, highlighting wide variations in vascular control between vascular beds. This study forms the basis for further investigation into the control of mesenteric blood flow in health and disease.

Mucosal regeneration and malignant change in inflammatory bowel disease

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Background Inflammatory bowel disease has a 14·8-fold increased cancer risk, by obscure mechanisms. This study tests the hypothesis that regenerating intestinal epithelium has increased sensitivity to DNA damage from luminal mutagens and initiation of carcinogenesis.
Methods A novel rodent model of regeneration was used, involving transplantation of crypt stem cell preparations (364 grafts). Metabolic defensive responses including Cytochrome P450 (Cyp), glutathione-S-transferase (GST) and uridine diphosphoglucuronosyl transferase (EGT) isoforms were assessed by Western blot in regenerating *versus* normal intestinal epithelium, after exposure to the mutagen benzo[a]pyrene. DNA damage was assessed quantitatively by ^{32}P-postlabelling for DNA adduct formation.
Results Epithelium at early stages of regeneration lacked metabolic defences (GSTA3, UGT in early regeneration *versus* Cyp2B, GSTA1/2, GSTA4, GSTP1, UGT in control) and sustained high levels of DNA adducts. DNA damage declined and metabolic defences recovered in late stage regeneration (e.g. mean(s.d.) 24 (17) adducts per 10^8 nucleotides in early regeneration *versus* 12 (9) adducts per 10^8 nucleotides in late regeneration ($P < 0·03$)).
Conclusion Intestinal epithelial regeneration provides a window of susceptibility to DNA damage which may initiate carcinogenesis.

Efficacy of laparoscopic ultrasonography in detecting liver metastases during colorectal cancer surgery

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Background The search for liver metastases before surgery forms an accepted part of colorectal cancer surgical practice. Intraoperative ultrasonography with manual palpation of the liver is the gold standard for screening for liver metastases. The purpose of this study was to demonstrate the efficacy of laparoscopic ultrasonography in detecting liver metastases at operation in comparison to conventional modalities.
Methods A prospective controlled study was undertaken. Some 73 consecutive patients undergoing laparoscopic colorectal resection for malignancy were recruited. Patients underwent preoperative liver ultrasonography and peroperative blinded laparoscopic ultrasonography using a flexible-tipped 6·5 MHz curved array transducer, capable of scanning the liver to a depth of about 10 cm.
Results Conventional ultrasonography was negative in all 73 patients. All patients have had Magnetic Resonance Imaging (MRI) scans at appropriate intervals except two who died at operation and two who could not tolerate MRI. Metastases were identified during initial peroperative laparoscopic inspection in one case and no additional lesions were found on laparoscopic ultrasonography in this patient. On nine other occasions the laparoscopic scan was abnormal. There were no false-negative laparoscopic ultrasonography examinations. The presence of metastases was confirmed in two patients diagnosed to have metastases on laparoscopic ultrasonography. Of the seven abnormal laparoscopic ultrasonography scans, three patients with suspicious lesions on laparoscopic ultrasonography were found to have metastases on MRI; in one it was deemed to be a cyst. Three remaining patients with suspicious lesions on laparoscopic ultrasonography were confirmed on serial MRI scans, to have benign lesions. Follow-up of all patients (median (interquartile range) 27·5 (18–38) months) has revealed liver metastases in three further patients at 12, 13 and 18 months. All three had normal MRI scans at the time of surgery.
Conclusion This study supports a role for laparoscopic ultrasonography in the detection of liver metastases and in the selection of patients for further sophisticated imaging. Laparoscopic ultrasonography is cheaper and better than conventional ultrasonography and is as sensitive as MRI.

Smooth muscle cell proliferation and *in vivo* implantation using gamma interferon-stimulated SV40 large T antigen is feasible

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Background Anal continence is frequently impaired by an internal sphincter deficit. Previous attempts to produce an anal 'neosphincter' using smooth muscle cell culture have been complicated by difficulties in cell proliferation and identification. The authors have previously demonstrated smooth muscle proliferation in cell culture using a system that drives cell proliferation in H2k mice. This is a transgenic mouse which has a DNA construct, consisting of a thermolabile mutant of the SV40 virus large T gene driven by a promoter integrated into its genome. Gamma interferon is activated by this promoter causing expression of large T driving cells into proliferation at 33°C. The mdx mouse does not possess the gene for dystrophin, so transplanted cells can be identified using antibodies against dystrophin in conjunction with smooth muscle markers. The authors have now assessed whether these *in vitro* proliferated smooth muscle cells are viable after subsequent *in vivo* implantation.
Methods Single cells isolated from the oesophagogastric junction were cultured using substrate attached explants derived from H2k transgenic mice. These cells were cloned and expanded *in vitro* by cell culture. They were then fixed and identified by immunocytochemistry for the expression of antigens consistent with smooth muscle. These smooth muscle clones were then pelleted into a fibrin clot and inserted either into the subcapsular kidney region or the denatured tibialis anterior muscle of mdx/nude host mice.
Results Implanted smooth muscle cells characterized by antibody staining could be identified under the renal capsule beyond 5 weeks and in the tibialis anterior beyond 3 months following implantation. However, some smooth muscle clones became transformed *in vivo* and subsequently formed tumours.
Conclusion Smooth muscle proliferation in cell culture and *in vivo* implantation is feasible, but the problem of neoplastic transformation has not been overcome.

Immunohistological modulation after nutritional supplementation with omega-3 essential fatty acids in patients with inflammatory bowel disease

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Background Patients with ulcerative colitis (UC) appear to have altered reactivity of gut-associated lymphoid tissue, with intense infiltration of the mucosa with immunocompetent cells. The authors have shown previously that dietary supplementation with the omega-3 essential fatty acids (EFAs) results in significant systemic immunosuppression. The aim of this study, therefore, was to evaluate the *in situ* effect of EFAs on distal UC.

Methods Patients received fish oil extract (eicosapentaenoic acid 3·2 g, docosahexaenoic acid 2·4 g) ($n=9$) or placebo ($n=9$) daily, in a double-blind manner for 6 months. Monthly assessment included (1) disease activity using clinical, sigmoidoscopic and histological scores and (2) immunohistochemical analysis (immunoglobulins, CD profiles) of rectal biopsies, using monoclonal antibodies and quantitative video analysis.

Results In the EFA group, there was improvement in disease activity and histological scores (median (range) 8 (3–10) and 5 (4–9) respectively) compared with pretreatment evaluation (16 (7–25) and 9 (7–10)) ($P<0·05$, Wilcoxon pairs test). Before supplementation, patients with distal UC ($n=18$) showed significantly higher numbers of immunoglobulin (Ig) G- and IgM-containing cells and cells expressing CD3 (T cells), CD20 (B cells) and human leucocyte antigen HLA DR, compared with healthy controls ($n=8$). After 6 months of supplementation, the two groups of patients showed the following results:

	EFA group ($n=9$)	Placebo ($n=9$)	P*
IgM (%)	25·7 (15·0 to 74·9)	34·1 (21·0 to 53·8)	0·04
CD3†	− 154 (− 173 to − 120)	− 32 (− 86 to 40)	0·01
CD20†	− 52 (− 82 to − 6)	− 5 (− 10 to 16)	0·04

Values are median (range). †Change from baseline. *Mann–Whitney *U* test

Conclusion This study has demonstrated suppression of *in situ* immune reactivity in patients with distal UC receiving EFA supplementation. This has important implications for therapy in patients with UC.

Ruptured abdominal aortic aneurysm is associated with raised levels of soluble tumour necrosis factor receptors

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Background Soluble tumour necrosis factor receptors (sTNF-Rs) are considered to be endogenous TNF antagonists. In sepsis, raised levels are associated with increased mortality rate. sTNF-Rs in haemorrhagic shock and early ischaemia–reperfusion injury have not been studied. Serum sTNF-R levels were examined in patients with ruptured abdominal aortic aneurysm (AAA).

Methods Sixteen patients undergoing repair of ruptured AAA and ten undergoing elective repair of intact AAA were studied. Type I and II sTNF-Rs were measured by enzyme-linked immunosorbent assay before operation (point 1), and immediately before (point 2), and 5 min (point 3) and 6 h (point 4) after aortic clamp release.

Results Type I sTNF-Rs were only significantly higher in patients with rupture at point 3 (median (range) 1·1 (0·2–3·5) *versus* 0·5 (0·2–1·1) ng ml^{-1}; $P<0·05$, Mann–Whitney *U* test). Data for type II sTNF-R are shown below.

Sample point	Ruptured AAA	Intact AAA	P*
1	4·0 (2·0–14·7)	2·1 (2·0–6·3)	< 0·05
2	3·3 (2·0–9·1)	2·1 (2·0–2·2)	< 0·001
3	3·2 (2·0–9·7)	2·1 (2·0–2·2)	< 0·001
4	10·0 (2·1–18·5)	2·5 (2·0–5·9)	< 0·001

Values are median (range). *Mann–Whitney *U* test

At point 4, type II sTNF-Rs were significantly higher in five patients with rupture who died (14·6 (9·7–18·0) ng ml^{-1}) than in 11 who survived (4·8 (2·1–18·5) ng ml^{-1}) ($P<0·05$).

Conclusion Ruptured AAA is associated with increased sTNF-R expression. Raised levels of type II sTNF-R are associated with increased postoperative mortality rate.

Both ETA and ETB receptors mediate proliferation in isolated human saphenous vein smooth muscle cells

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Background Smooth muscle cell proliferation is central to the development of intimal hyperplasia. Endothelin has mitogenic effects and is implicated in the aetiology of intimal hyperplasia. However, there is tissue, species and functional variation in cell endothelin receptor expression. As a result it is not clear which receptors mediate smooth muscle cell proliferation in human saphenous vein grafts. The aim of this study was to determine which receptors promote endothelin-induced smooth muscle cell proliferation in human saphenous vein.

Methods Smooth muscle cells explanted from human long saphenous vein were used at second passage. These cells were seeded into multiwell plates at a concentration of 1×10^4 per ml and growth arrested for 72 h in 0·4 per cent fetal calf serum (FCS). They were then incubated in minimal growth promoting media (2·5 per cent FCS) to which was added endothelin 10 nmol^{-1} with or without an endothelin receptor antagonist. These were the mixed ETA/ETB antagonist Bosentan (10 μmol^{-1}), the ETA antagonist BQ123 (3 μmol^{-1}), and the ETB receptor antagonist BQ788 (3 μmol^{-1}). A similar series of cells cultured in 2·5 per cent and 15 per cent FCS acted as negative and positive controls respectively. Cell counts were performed in duplicate every second day and the drugs and media were replaced in the remaining wells. Each experiment lasted for 12 days and was repeated in cells from eight different patients.

Results Cell proliferation was expressed as a ratio of the amount of growth of each group to the amount of growth in the 2·5 per cent FCS control. Endothelin produced a median (range) growth ratio of 1·5 (0·9–1·9). Bosentan produced a median (range) growth ratio of 0·9 (0·6–1·5). That of BQ788 and BQ123 was 0·9 (0·7–1·3) and 1·0 (0·8–1·3) respectively. All the antagonists significantly reduced endothelin-induced smooth muscle cell proliferation ($P=0·02$, Wilcoxon test) but there was no significant difference between each antagonist.

Conclusion Endothelin-induced proliferation of smooth muscle cells isolated from human saphenous vein can be mediated via both ETA and ETB receptors.

Hyperhomocysteinaemia is associated with abdominal aortic aneurysm

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Background Hyperhomocysteinaemia is a recognized risk factor for premature peripheral vascular disease. No previous study has examined an association with abdominal aortic aneurysms (AAA), despite anecdotal reports of aneurysms in patients with homocystinuria. The aim of this case-controlled study was to determine the prevalence of hyperhomocysteinaemia in patients with AAA.

Methods Plasma was separated and frozen within 1 h of venepuncture from fasting subjects and controls. Homocysteine (HCY) was measured in a high-pressure liquid chromatography assay with electrochemical detection. Control results were logarithmically transformed to give a reference range (mean ± two standard deviations) of 8·86–14·25 $\mu\text{mol l}^{-1}$.

Results Results are as follows:

	AAA ($n = 14$)	Controls ($n = 30$)
HCY (μmol l^{-1})	17·5 (12·90–18·50)*	11·30 (9·37–14·07)

Values are median (interquartile range). *$P = 0\cdot0109$ *versus* controls (Mann–Whitney *U* test)

Hyperhomocysteinaemia (HCY greater than 14·25 μmol l^{-1}) was present in 11 of 14 patients with AAA, but only seven of 30 controls ($\chi^2 = 8\cdot349$, $P = 0\cdot001$).
Conclusion This is the first report of an association between hyperhomocysteinaemia and AAA. More patients are required for confirmation, but these findings raise the possibility of managing small aneurysms, and patients at risk with vitamin supplements.

Increased expression of the endothelial specific Tie-1 receptor by hypoxia

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Background Tissue ischaemia is a common and important problem, especially in the lower limb. A novel treatment currently showing promise in clinical trials is to revascularize the limb by stimulating new blood vessel growth with angiogenic growth factors, notably vascular endothelial growth factor (VEGF). A major limitation of this approach is that VEGF only activates initial stages of vessel growth and produces immature vessels prone to thrombosis and leakage. Maturation to patent vessels requires activation of another set of receptors, those for Tie. Tie-1 and Tie-2 are endothelial cell-specific tyrosine kinase receptors. However, nothing is known about the factors which control the level of Tie-1 or its ligands in the ischaemic or revascularizing limb. The aim of the study was to determine whether expression of Tie-1 or its ligands is modulated in endothelial cells by hypoxia and VEGF, conditions which are encountered in the ischaemic and VEGF revascularizing limb.
Methods Bovine aortic endothelial cells were subjected to hypoxic conditions for varying lengths of time (0–24 h). Tie-1 expression was analysed by Western blotting.
Results Tie-1 expression increased almost fourfold ($P = 0\cdot017$) after 24 h of hypoxia. A similar increase was observed following stimulation with VEGF. Using a technique based on the measurement of Tie-1 ectodomain binding, Tie-1 ligand expression was shown to be insensitive to hypoxia.
Conclusion These data demonstrate, for the first time, that hypoxia and VEGF upregulate the expression of Tie-1 in vascular endothelium. If this occurs *in vivo*, it suggests that existing and newly forming blood vessels in the ischaemic limb are likely to have increased sensitivity to Tie ligands. The ability to activate this system, with either endogenous or exogenous ligand, is likely to lead to vessel maturation and the formation of patent vessels.

Cerebral cytokine production during carotid surgery: markers of a significant ischaemic insult

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Background The proinflammatory cytokines interleukin (IL) 6 and IL-8 are produced as part of the acute-phase response to ischaemia–reperfusion in skeletal muscle and myocardium and may influence both the local and systemic leucocyte response to the ischaemic insult. It is unknown whether a similar response occurs following temporary occlusion of the carotid vessels during carotid endarterectomy (CEA).
Methods Cerebral cytokine production was assessed in venous samples obtained from the ipsilateral jugular bulb before cross-clamping the carotid vessels (T_0) and at 4 h (T_4) and 24 h (T_{24}) following reperfusion in 18 patients undergoing CEA (nine under general anaesthesia, nine under local anaesthesia). Il-6 and IL-8 levels were compared with systemic levels in 20 controls (minor elective surgery, no ischaemia–reperfusion) measured following induction of general anaesthesia and at the same times after operation.
Results

	IL-6		IL-8	
	Control	CEA	Control	CEA
T_0	2·0(0·4)	10·5(3·7)	6·1(1·1)	0·8(0·4)
T_4	29·9(5·7)	98·2(24·0)	8·8(2·5)	11·6(3·6)
T_{24}	26·0(3·9)	68·3(8·5)	11·7(4·8)	22·1(4·7)

Values are mean(s.d.)

Following CEA there was a significant rise in cerebral IL-6 and IL-8 production compared with precross-clamp levels (T_4 and T_{24}, $P < 0\cdot0001$). These levels were also significantly higher than those in the control patients (T_4 IL-6: $P < 0\cdot0005$; T_{24} IL-6: $P < 0\cdot0001$, IL-8: $P < 0\cdot02$). There was a non-significant trend ($P < 0\cdot2$) to suggest that cytokine production, and therefore the ischaemic injury, was less in patients given local anaesthesia for CEA.
Conclusion These results confirm that CEA results in significant cerebral ischaemia. The effectiveness of potential cerebral protection strategies could be assessed by determining the cytokine response to surgery.

Smoking and shear stress-induced endothelial cell anoikis may be prevented by the amino acid taurine

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Background Vascular endothelial cells (ECs) require attachment to the extracellular matrix (ECM) for growth and survival. Loss of this anchorage by disruption of the ECM results in anoikis, or apoptosis from lack of anchorage. Anoikis may be the result of either mechanical or chemical stresses. Smoking-induced endothelial damage has previously been shown to increase the number of circulating ECs. It is not clear whether such cells are apoptotic or necrotic. Cigarette smoking increases shear stress (SS) and oxidant-mediated EC damage. The authors have previously demonstrated that the amino acid taurine can reverse the abnormal function of ECs in smokers and can prevent oxidant-mediated EC apoptosis *in vitro*. It was hypothesized that (1) increases in SS *in vitro* result in increased EC death by apoptosis and that (2) taurine treatment of young smokers may prevent the increase in apoptosis induced by cigarette smoking.
Methods Seven healthy smokers with a self-reported smoking history of 2 pack-years and 11 control non-smoking subjects were studied. Circulating carcasses of ECs were isolated from peripheral blood samples and counted by the method of Hladovec and Rossman. Cells were stained with fluorescein-labelled antihuman factor VIII monoclonal antibody to confirm the identity of these ECs. Apoptosis of the cells was assessed with the terminal deoxynucleotidyl transferase-mediated 2′-deoxyuridine 5′triphosphate nick end labelling technique. Samples for the estimation of EC desquamation were taken before and after inflation and subsequent deflation of a cuff to 200 mmHg for 2 min ($n = 8$), and before and after treatment of smokers with taurine 1·5 g day^{-1} for 5 days ($n = 7$).

Results

	Baseline	Increase in SS	Non-smokers	Smokers	Smokers + taurine
No. of apoptotic cells per 0·9 μl	1·06(0·29)	2·4(0·77)*	0·93(0·42)	3·29(1·43)†	1·11(0·59)‡

Values are mean(s.d). *$P = 0·002$ *versus* baseline; †$P = 0·02$ *versus* non-smokers; ‡$P = 0·006$ *versus* smokers

Conclusion This study reveals that acute increases in SS and chronic cigarette smoking induce anoikis. The amino acid taurine has the capability to prevent EC apoptosis and may have an important role in EC functioning and survival.

Ruptured abdominal aortic aneurysm is associated with inhibition of systemic fibrinolysis

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Background It has been suggested that ruptured abdominal aortic aneurysm (AAA) is associated with systemic fibrinolysis and that haemorrhage may be limited by antifibrinolytics such as aprotinin. For the first time, thrombin generation and systemic fibrinolysis in patients undergoing repair of ruptured and intact AAA was examined.
Methods Ten patients undergoing repair of ruptured AAA and nine patients undergoing repair of intact AAA were studied. Tissue plasminogen activator (t-PA) activity, plasminogen activator inhibitor (PAI) activity and prothrombin fragment (PF) 1 + 2 were measured before operation, immediately before and 5 min after aortic clamp release and 24 h after operation.
Results Before operation rupture was associated with significantly increased PAI activity (median (range) 36·5 (20·6–38·8) *versus* 8·2 (3·2–21·7) units ml^{-1} for non-rupture; $P < 0·001$, Mann–Whitney U test) and significantly decreased t-PA activity (median (range) 0·12 (0·06–0·43) *versus* 0·49 (0·14–3·2) units ml^{-1} for non-rupture; $P < 0·01$). In both groups there was a significant increase in PF 1 + 2 above the normal range (0·4–1·1 nmol l^{-1}) but this was significantly greater in patients with rupture (median (range) 9·0 (5·4–11·6) *versus* 2·2 (0·7–7·1) nmol l^{-1}; $P < 0·001$). These changes persisted throughout the course of surgery.
Conclusion Ruptured AAA is associated with systemic thrombin generation and inhibition of systemic fibrinolysis. These data do not support the use of antifibrinolytic therapy in patients operated for ruptured AAA.

Genetic analysis of breast tumours by comparative genomic hybridization

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Background Molecular genetic studies have identified several mutations, chromosomal deletions and amplifications in breast cancer. However most techniques limit analysis to one gene or chromosomal region. This study concentrated on the entire genome using a new technique, comparative genomic hybridization (CGH).
Methods CGH is based on the competitive hybridization of two differentially labelled DNA samples to normal metaphase spreads. Tumour DNA is labelled with a green fluorochrome and normal reference DNA is labelled with a red fluorochrome. Image analysis compares the intensity of the green to red staining and calculates the ratio thus allowing copy number changes to be identified throughout the genome. Fifteen consecutive breast tumours were studied. All were staged according to standard tumour node metastasis classification. Reference DNA was extracted from the patients' lymphocytes and, in order to distinguish between somatic and germline mutations, the tumour specimens were also compared using standard reference DNA (Vysis).
Results Recurrent regions of amplification involved 1q (12 of 15), 3q (nine of 15), 5q (eight of 15), 12p (eight of 15) and 20p (nine of 15). The means(s.d.) number of amplifications per tumour was 12·7(6·4), involving 8·5(3·3) chromosomes in each tumour. Recurrent regions of deletion involved 17p (seven of 15) and 15p (seven of 15). The mean(s.d.) number of deletions per chromosome was 10(4·2), involving 5·1(3·8) chromosomes in each tumour. The greatest number of aberrations (30) was found in a T$_4$ tumour. The sites of most of the copy number changes were distinct from those of currently known cancer genes.
Conclusion These results have implications for future studies and suggest a multistep and multigene involvement in breast carcinogenesis.

Lack of correlation between failure of gut barrier function and sepsis following major surgery

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Background Failure of the gut mucosal barrier to exclude bacteria and endotoxin from the portal and systemic circulation is incriminated in the development of sepsis and multiple organ failure. There are compelling animal data to support this thesis, but corroborative clinical evidence is sparse. Patients undergoing major resectional surgery were investigated to determine the relationship of circulating endotoxin to intestinal permeability and outcome of sepsis.
Methods Fifty-six patients undergoing curative resectional surgery for upper gastrointestinal malignancy were monitored for 30-day septic morbidity (intra-abdominal abscesses/empyema and pneumonia). Intestinal permeability, C-reactive protein (CRP) and serum immunoglobulin (Ig) antiendotoxin (EndoCAb) antibodies were determined before operation (PRE) and on postoperative day 1 (POD1).
Results

	Sepsis ($n = 20$)	No sepsis ($n = 36$)	P†
Intestinal permeability*			
PRE	0·06(1·16)	0·06(0·18)	0·66
POD1	0·18(3·83)	0·18(0·87)	0·53
Serum CRP (mg l^{-1})			
PRE	7·7(26·1)	10·5(40·3)	0·81
POD1	125·8(38·7)	117·1(45·2)	0·77
IgM EndoCAb (MU ml^{-1})			
PRE	96(116)	154(139)	0·27
POD1	85(62)	92(75)	0·49

Values are median (s.d.). *Lactose : mannitol ratio. †Mann–Whitney U test

There was no significant difference in intestinal permeability, CRP and endotoxin exposure before operation and on the day after surgery between the two groups. Logistic regression analysis did not identify a significant association between intestinal permeability, CRP and level of endotoxin with septic outcome.
Conclusion Patients who developed sepsis following major upper gastrointestinal surgery did not differ before surgery with respect to intestinal permeability, acute-phase response and endotoxin exposure, compared with patients who did not develop sepsis. Moreover, the magnitude of change in all the parameters on the first postoperative day did not differ in the two groups. There is no support from this study to incriminate the measured changes

in gut barrier function or endotoxin exposure to the development of sepsis.

Dynamic real-time magnetic resonance imaging for occult groin pain

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Background Persistent groin pain without clinical signs is a difficult diagnostic problem. Some patients have occult inguinal hernias, but others have musculotendinous injuries not necessarily requiring surgery. No existing imaging modality is sufficiently sensitive to reliably distinguish the two. Therefore the negative surgical exploration rate is high. Interventional magnetic resonance (IMR) units allow real-time imaging in physiological positions and during muscular exertion. This study aimed to develop an IMR imaging technique to aid differentiation of the conditions.
Methods Ten patients (eight male, two female) were studied in a 0·5-T General Electric Signa SP10 IMR apparatus. Three had obvious inguinal hernias, one a cord haematoma following previous hernia repair and six occult groin pain without physical signs. Static imaging (T1/T2 fast spin echo (FSE), fast gradient recalled (FSPGR) and short tau inversion recovery (STIR)) was performed with the patient supine for detailed anatomical examination and differentiation of structural from inflammatory lesions. Dynamic real-time imaging (FSPGR, acquisition time 2 s) was then performed with the patient supine and kneeling at rest and during a Valsalva manoeuvre.
Results All patients tolerated the procedure. The sac and defect in the fascia transversalis (FT) were clearly seen in T1 FSE and FSPGR images in the three obvious hernias. The sacs could be seen moving in and out of the defect on dynamic imaging. STIR images were normal. The cord haematoma was differentiated from recurrent hernia by a normal FT and high signal on T2 and STIR imaging. Of the remaining six patients without physical signs imaging revealed one indirect sac in a 30-year-old man which was confirmed at surgery. In one man (aged 31 years) both imaging and surgical exploration revealed no abnormality. The remaining two men (aged 29 and 32 years) had high STIR signals in the posterior rectus, consistent with muscular injury, and no hernial defect. The remaining two women (aged 43 and 57 years) had high STIR signals at the inguinal ligament's insertion on the pubis. These patients were treated conservatively.
Conclusion This study has shown that dynamic IMR imaging can detect and differentiate both clinically apparent and occult groin hernias from musculotendinous injuries. This may reduce the negative surgical exploration rate for such patients in the future.

Incidence of anal sphincter injury during childbirth has been overestimated

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Background Anal sphincter injury is thought to be present in nearly half of multiparous women who have had vaginal deliveries. Symptoms of such trauma are thought to affect nearly a quarter of multiparous women. This not borne out by current clinical practice.
Methods Eighty pregnant women were assessed antenatally using a symptomatic questionnaire, endoanal ultrasonography and anorectal manometry. They were re-evaluated between 6 and 12 weeks after delivery. All examinations were carried out by the same investigator. All modes of delivery were encountered.
Results Antenatally, there were no instances of faecal urgency or incontinence. Sonography revealed intact sphincters in all women and anal canal resting pressure and squeeze pressure (MSP) were within this laboratory's normal range. Two women reported postnatal faecal urgency; there were no new sphincter defects identified and postnatal manometry results were not significantly different to antenatal values.

Over a 6-week period and using the same methods of evaluation, a further 159 women were assessed within 72 h of delivery. Of this group, one woman developed faecal urgency but there were no reports of faecal incontinence. No third-degree tears occurred.

	Vaginal ($n = 114$)	Forceps ($n = 6$)	Caesarian section ($n = 39$)
Sonographic defects	10 (8·8)	5	0

Values in parentheses are percentages

Median MSP was significantly lower in the 15 women who sustained an anal sphincter injury compared with that in the 144 who did not (interquartile range 35–58) *versus* 78 (65–103) cmH$_2$O; $P < 0·0005$).
Conclusion These results indicate that anal sphincter trauma is an uncommon complication of vaginal delivery and symptoms of sphincter dysfunction affect less than 1 per cent of these deliveries. They provide compelling evidence that previous work has overestimated the incidence and should be updated.

Prognostic significance of flap recurrence following mastectomy for breast cancer

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Background The management of flap recurrence after mastectomy for breast cancer remains controversial.
Methods Between 1976 and 1991, 3310 mastectomies were performed for breast cancer in one unit. An overall recurrence rate of 9·7 per cent was observed with a mean follow-up of 12·2 (range 5–20) years. Flap recurrences following mastectomy for T_1–T_3 tumours without radiotherapy were identified ($n = 256$) and were examined to determine the factors predicting survival after flap recurrence. Single spot recurrence was treated by simple excision whereas those with multiple spot and field change recurrence received radiotherapy and systemic hormone therapy or chemotherapy. Statistical analysis was by χ^2 test or Student's *t* test.
Results Nodal status at presentation ($P < 0·05$), time to recurrence and presence of concurrent disease influenced survival. Five-year survival for women with concurrent disease at the time of flap recurrence (45 per cent) was poor compared with that in women without concurrent disease (55 per cent) ($P < 0·0001$). Early recurrence (within 12 months of primary surgery) correlated with poor survival ($P < 0·0001$) even allowing for concurrent disease ($P < 0·001$). The type of recurrence (single spot, multiple spot or field of change) did not influence survival and the frequency of concurrent disease with flap recurrence did not depend on the time interval between diagnosis and recurrence.
Conclusion Flap recurrence occurring in the first year following mastectomy for breast cancer predicts poor survival. All flap recurrences have a high chance of concurrent systemic disease and therefore all require systemic therapy.

Importance of negative microscopic margins in the multimodality therapy of oesophageal cancer

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Background Positive microscopic margins after major cancer surgery for cure adversely affect prognosis. Multimodal therapy (neoadjuvant chemoradiotherapy) prolongs survival in patients with oesophageal cancer compared with surgery alone. It is possible that the benefit of this neoadjuvant approach is in part due to reduced involvement of resection margins and multimodal therapy may alter the disease course when resection margins are involved.

Methods A pathological re-review was performed of 212 patients with oesophageal carcinoma who underwent multimodal therapy ($n = 104$) or surgery alone ($n = 108$), as part of randomized clinical trials. Patients within both groups with microscopic margin involvement were compared for disease recurrence.

Results Margins were microscopically involved in 13 per cent of patients treated by multimodal therapy compared with 38 per cent of those who had surgery ($P = 0\cdot0001$). Twenty-six per cent had a complete pathological response. At a median follow-up of 16 months, patients with clear margins had a recurrence range of 43 per cent (multimodal) and 73 per cent (surgery) ($P = 0\cdot0003$). There was significantly reduced recurrence in patients with positive margins receiving multimodal therapy (38 per cent) compared with patients who had surgery only (89 per cent) ($P = 0\cdot007$).

Conclusion The benefit of multimodality therapy in patients with clear margins remains highly significant when patients with positive margins are excluded. Neoadjuvant therapy increases the number of curative resections compared with surgery alone. The consequences of involved margins are also reduced, with decreased rates of recurrence, suggesting that the neoadjuvant approach may alter the biology of residual tumour cells.

Adenoviral targeted delivery of a suicide gene to the liver: an antineoplastic strategy

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Background Cytosine deaminase (CD) is a bacterial enzyme that converts the non-toxic agent 5-fluorocytosine (5-FC) to the active chemotherapeutic agent 5-fluorouracil (5-FU). Adenoviral vector (Ad.) containing the CD transgene (Ad.CD) can be used to generate high local concentrations of 5-FU, when combined with systemic 5-FC administration. Using this strategy in a flank tumour model of murine pancreatic cancer the authors have previously demonstrated limited efficacy *in vivo* after direct intratumoral injection of Ad.CD. It was postulated that efficacy is limited because of efflux of Ad. from the tumour into the circulation after direct intratumoral injection, followed by preferential uptake of circulating Ad. by the liver, which has numerous Ad. receptors. It was hypothesized that Ad. hepatotropism could be used to treat hepatic tumours using the Ad.CD, 5-FC strategy.

Methods Mice were randomized into four groups ($n = 6$). Solitary hepatic tumours were established by injecting 10^5 Pan02 cells into the right lobe of liver. At 48 h Ad.CD was administered intravenously. At 72 h 5-FC was administered daily for 6 days. Mice were killed on day 15, and tumour growth compared with that in controls.

Results The figure shows the effect of Ad.CD on solitary hepatic tumour growth. Treatment with Ad.CD and 5-FC resulted in significant inhibition in the growth of Pan02 within the liver ($P < 0\cdot005$, analysis of variance).

Conclusion These data demonstrate that adenoviral hepatotropism may have potential use for the treatment of hepatic tumours.

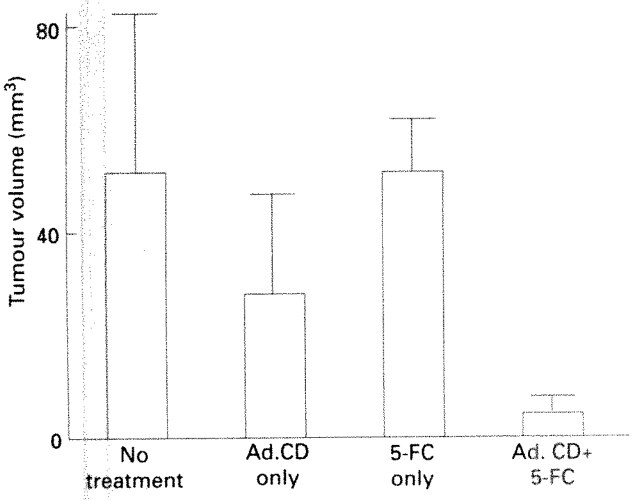

Fig. 1

Fluorescence detection of dysplasia and cancer

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Background 5-Aminolaevulinic acid (ALA) is a fluorescent photosensitizer which has been used to enhance the early detection of cancer and dysplasia with encouraging results. However, it has not been evaluated in the upper gastrointestinal tract where it may aid the endoscopic surveillance of precancerous conditions such as Barrett's oesophagus. The result of an ongoing study of ALA-induced fluorescence in the upper gastrointestinal tract is reported.

Methods Informed consent from patients and local ethics committee approval for the study was obtained. Thirteen patients with histologically confirmed mucosal cancer (eight oesophageal, five gastric) undergoing surgery were studied. Each patient received oral ALA 3–$20\,\mathrm{mg\,kg^{-1}}$ 4–9 h before surgery. Fluorescence was stimulated on specimens and correlated with histology (gold standard). Cancer and severe dysplasia were grouped together as abnormal; Barrett's metaplasia was grouped with normal.

Results The spectroscopic characteristics of fluorescence confirmed tissue uptake of ALA. There were 105 random biopsies from fluorescent and non-fluorescent mucosa (40 normal, 12 Barrett's, eight severe dysplasia and 45 cancer). All biopsies from normal and Barrett's mucosa exhibited fluorescence and all except one specimen of severe dysplasia and five cancers did not fluoresce. Based on this, the sensitivity and specificity of negative fluorescence for predicting cancer and severe dysplasia were 89 per cent and 100 per cent respectively.

Conclusion Previous studies in the skin, lung and bladder have demonstrated selective fluorescence in abnormal tissues. However, in this study fluorescence was absent in the vast majority of abnormal mucosas and present in all normal mucosa samples. The presence or absence of fluorescence predicted cancer and severity with a high degree of accuracy. Therefore, ALA-induced fluorescence may have a potential role in the endoscopic surveillance of patients at a high risk of developing upper gastrointestinal cancer.

Tumour length predicts response to neoadjuvant chemoradiotherapy in oesophageal adenocarcinoma

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Background Multimodality therapy (neoadjuvant chemoradiotherapy) confers a survival advantage compared with surgery alone in oesophageal adenocarcinoma. This management strategy could be further optimized if the factors predicting response or resistance to this neoadjuvant approach were elucidated. With this aim a detailed clinical, pathological and treatment re-review was performed, comparing neoadjuvant responders with non-responders.

Methods Patients ($n=63$) were categorized as responders ($n=32$) or non-responders ($n=31$) to multimodality therapy based on pathological evaluation of the resected specimen. Responders (T_0N_{0-1}, pT_1N_{0-1}, pT_2N_0) were compared with non-responders (pT_2N_1, pT_3N_{0-1}) for the following variables: age, sex, initial tumour length and differentiation, associated intestinal metaplasia, weight loss (more than 5 per cent before treatment), initial serum albumin level, and post-treatment radiation fibroblasts, and tissue and vascular fibrosis.

Results Initial tumour length (mean 4·2 (responders) *versus* 6·6 cm (non-responders); $P=0{\cdot}0063$, Wilcoxon test) was the sole factor significantly associated with lack of response to the neoadjuvant regimen. The presence and intensity of post-treatment vascular and fibroblast changes ($P=0{\cdot}3$, Fisher's exact test) did not correlate with response.

Conclusion The mural extent of tumour was significantly associated with treatment response. This may reflect a tumour–host relationship for larger tumours promoting catabolism and countering effective treatment responses.

Cytokine gene polymorphism and disease severity in acute pancreatitis

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Background Monocyte proinflammatory cytokine secretion mediates disease severity in acute pancreatitis. Cytokine secretion is determined by a combination of environmental and genetic factors. Polymorphisms identified in the tumour necrosis factor (TNF) and interleukin (IL)-1 gene loci correlate with levels of monocyte cytokine secretion *in vivo* and are markers of disease severity in inflammatory conditions. For each condition allele 2 appears important. This study assessed whether these cytokine gene polymorphisms correlate with disease severity in acute pancreatitis.

Methods Leucocyte DNA was isolated from a consecutive series of 124 patients with acute pancreatitis. Molecular techniques were used to determine TNF, IL-1β and IL-1 receptor antagonist genotypes. Disease severity as defined by Atlanta criteria was mild in 78, severe in 42 and four had local complications alone. The aetiological agent was gallstones in 46, alcohol in 42, idiopathic in 22 and 14 'other'. Statistical analysis was by χ^2 test (contingency tables for categorical data).

Results There were no significant differences in genotype frequency distributions nor were there significant differences in the distribution of TNF allele 2, IL-1β allele 2 and IL-1 receptor antagonist allele 2. There was no significant difference in the distribution of these alleles between patients with mild disease and those with severe disease.

Conclusion These results show no association between the cytokine gene polymorphisms studied and disease severity in acute pancreatitis.

Membrane-type matrix metalloproteinase 1 expression in gastric cancer: a new target for therapy

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Background The matrix metalloproteinases (MMPs) are a family of proteolytic enzymes which regulate extracellular matrix turnover and are implicated in tumour growth and metastasis. Their inhibition is an attractive therapeutic concept. Studies of broad-spectrum MMP inhibitors (MMPIs) in advanced gastric cancer have been limited by side-effects. A selective inhibitor might be more efficient. Reverse transcriptase–polymerase chain reaction was used to quantify the relative amounts of MMPs, membrane-type MMPs (MT-MMPs) and tissue inhibitors of MMP (TIMPs) in gastric tumours and the findings were confirmed using gelatin zymography.

Methods Gastric carcinoma tissue and normal mucosa were taken from 20 resections. Messenger RNA (mRNA) was extracted and reverse transcribed to complementary DNA. Competitive polymerase chain reaction was performed with a gene-specific external standard. Results were normalized to glyceraldehyde-3-phosphate dehydrogenase. Zymography was used to show the active and inactive forms of MMP-2 and MMP-9.

Results

mRNA	Median tumour	Median normal	P*
MMP-2	$7{\cdot}4\times10^{-7}$	1×10^{-8}	0·0166
MMP-9	$5{\cdot}8\times10^{-6}$	1×10^{-8}	n.s.
MT-MMP-1	$6{\cdot}5\times10^{-4}$	1×10^{-8}	0·0267
TIMP-1	$5{\cdot}3\times10^{-2}$	1×10^{-8}	n.s.
TIMP-2	$1{\cdot}3\times10^{-3}$	$1{\cdot}8\times10^{-3}$	n.s.

n.s., Not significant. *Wilcoxon test

Gelatin zymography showed both forms of MMP-2 and MMP-9 in the tumour samples but inactive species only in the normal mucosa.

Conclusion These techniques give a relative level of each enzyme within a tumour sample. Comparing tumour with normal tissue reveals a significant difference for MMP-2 and its activator MT-MMP-1. Zymography demonstrates active MMP-2 in the tumours only. An appropriate MMPI might be one specifically against MT-MMP-1. This would prevent the subsequent activation of pro-MMP-2, which has a well established role in the process of tumour growth and metastasis.

TPR-MET oncogenic rearrangement is involved early in gastric carcinogenesis

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Background c-*met*, which encodes the hepatocyte growth factor receptor, can occur in a truncated mutant form spliced to a translocated promoter region (TPR-MET). This form of the receptor is constitutively activated, and is widely believed to be important in carcinogenesis, largely from evidence obtained *in vitro* and transgenic expression in mice. The relative frequency of TPR-MET expression in human gastric carcinomas and normal mucosa is unknown. TPR-MET messenger RNA expression in gastric carcinomas, associated 'normal' mucosa and mucosa from patients with histologically and bacteriologically normal stomachs was studied.

Methods Amplifiable complementary DNA was obtained by reverse transcription of transfer RNA extracted from *N*-methyl-*N*′-nitroso-guanidine human osteosarcoma cells, 35 gastric cancers, 28 associated 'normal' and 18 histologically normal stomachs. 'Hot-start' nested polymerase chain reaction (PCR) was performed, and the products electrophoresed, stained and examined under ultraviolet light. The PCR products were sequenced.

Results Results are shown in the *Table*.

	TPR-MET positive	TPR-MET negative	*P*
Gastric cancer ($n = 35$)	26	9	
Associated normal mucosa ($n = 28$)	19	9	0·13*, 0·26†
Normal mucosa ($n = 18$)	8	10	0·04

*Fisher's exact test, †Paired *t* test

Conclusion TPR-MET rearrangement is found in a high proportion of gastric cancers and associated non-malignant mucosa. It is frequently present in normal mucosa without *Helicobacter pylori* infection. These findings implicate TPR-MET in the very early stages of human gastric carcinogenesis.

Reduction in membranous expression of β-catenin predicts poor survival in gastric cancer

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Background β-catenin, a component of the E-cadherin–catenin cell adhesion complex, also plays a separate intracellular signalling role, interacting with APC (adenomatous polyposis coli) protein. Intracellular accumulation of β-catenin is common in colorectal neoplasia. β-catenin abnormalities are associated with poor survival in gastric cancer, but previous studies have not differentiated between membrane-associated and intracellular β-catenin. The aim of this study was to determine which type of β-catenin expression abnormalities correlate with survival in gastric cancer.

Methods Immunoperoxidase staining of paraffin-embedded sections from 40 gastric cancers was performed for E-cadherin, and α- and β-catenins using microwave unmasking and a biotin–avidin technique. Clinical data were obtained from case records.

Results Abnormalities of intracellular β-catenin staining were rare in gastric cancer (two of 40). Reduced membranous expression occurred in ten of 12 diffuse and eight of 28 intestinal tumours ($P = 0{\cdot}0014$). It was associated with poor differentiation ($P = 0{\cdot}0015$) and short survival ($P = 0{\cdot}032$), but not with age, sex, tumour size or nodal status. Reduced E-cadherin membrane expression was associated with lymph node metastasis ($P = 0{\cdot}02$). Neither E-cadherin nor α-catenin expression correlated with survival.

Conclusion Reduced membranous expression of β-catenin predicts poor prognosis in gastric cancer, whilst ectopic intracellular expression is rare. The apparent differences in β-catenin expression from those found in colonic cancer merit further study.

Loss of heterozygosity on chromosome 17p predicts carcinogenesis progression in patients with Barrett's oesophagus

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Background Endoscopic surveillance for adenocarcinoma in patients with Barrett's oesophagus is time consuming and costly, with one cancer detected in every 175 patient-years of follow-up. Genetic abnormalities, including loss of heterozygosity (LOH) at the sites of tumour suppressor genes, have been detected in malignant and premalignant Barrett's oesophagus, and the aim of this study was to determine the feasibility of LOH analysis as a method of identifying which patients with Barrett's oesophagus are at greatest risk of adenocarcinoma, and therefore in greatest need of regular endoscopy.

Methods LOH analysis was performed by polymerase chain reaction and gel electrophoresis on endoscopic biopsies from 48 patients in a Barrett's surveillance programme. Fourteen microsatellite primers located at known or putative tumour suppressor genes on chromosomes 3p (*VHL*), 5q (*APC*), 9p (*CDKN2*), 11p, 13q (*Rb*), 17p (*p53*), 17q and 18q (*DCC*), and shown previously to detect frequent LOH in oesophageal adenocarcinomas, were used in the analysis. The patients were followed endoscopically and histologically for a median of 3·5 years.

Results LOH was detected in nine patients. Three patients with LOH on chromosome 5q or 9p did not progress beyond metaplasia. LOH on chromosome 17p was detected in six patients, all of whom demonstrated carcinogenesis progression (low-grade dysplasia (four patients), high-grade dysplasia (one) and adenocarcinoma (one)).

Conclusion LOH on chromosome 17p identifies patients with Barrett's oesophagus at greatest risk of carcinogenesis progression, and therefore at greatest need of regular endoscopic surveillance.

Intestinal metaplasia at the oesophagogastric junction and cardia in symptomatic patients

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Background The incidence of adenocarcinoma around the oesophagogastric junction (OGJ) is increasing, and many of these cancers arise in association with areas of intestinal metaplasia (IM). Barrett's oesophagus, characterized by IM over more than 3 cm of the oesophageal lining, is associated with a significantly increased risk of developing adenocarcinoma. Metaplastic changes may involve shorter segments of the lower oesophagus (less than 3 cm) and may not be detected on endoscopy or with routine histological techniques. The aims of this study were to define and compare metaplastic changes at the OGJ with those at the cardia and to identify the true prevalence of Barrett's oesophagus, short-segment Barrett's and microscopic IM in a population of symptomatic patients attending for open access endoscopy.

Methods Some 225 patients had gastroscopy, and any clinically indicated biopsies were taken. In addition, three further sets of endoscopic biopsies were taken from each patient, at 3-cm intervals, from the cardia, the OGJ and the distal oesophagus. These were all examined using haematoxylin and eosin, Alcian Blue/periodic acid–Schiff and high iron diamine/Alcian Blue stains, to define IM.

Results Of 225 patients, eight (3·6 per cent) had carcinoma, eight (3·6 per cent) had conventional long-segment Barrett's oesophagus, 15 (6·7 per cent) showed endoscopic short-segment Barrett's change, and there was no endoscopic Barrett's in 194 (86·2 per cent). Of the latter, 34 (17·5 per cent) had IM at the OGJ and nine (4·6 per cent) at the cardia on haematoxylin and eosin staining. Acid mucin stains detected IM at the OGJ in 135 (69·6 per cent) and at the cardia in 75 (38·7 per cent). Patterns of IM at the OGJ differed from those seen at the cardia. Some 90 per cent of patients with IM detectable by haematoxylin and eosin staining were taking strong acid suppression, compared with 72·8 per cent overall.

Conclusion IM is very common at the OGJ and cardia, with marked differences in incidence and characteristics between the two sites. The relationship of IM at the OGJ to development of carcinoma is yet to be determined.

Endoscopic argon beam plasma coagulation in the restoration of squamous lining in Barrett's oesophagus

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Background Barrett's oesophagus is associated with a significantly increased risk of development of oesophageal adenocarcinoma. Replacing columnar epithelium by the normal squamous lining in this condition offers the possibility of decreasing risk of degeneration to invasive adenocarcinoma. This study aimed to establish the feasibility of argon beam plasma coagulation (ABPC), in conjunction with control of gastro-oesophageal reflux, to restore the squamous lining.

Methods Some 28 patients with Barrett's oesophagus (four low-grade dysplasia, three high-grade) were recruited from the authors' surveillance programme, and underwent endoscopic ABPC. Gastro-oesophageal reflux was controlled with antireflux surgery in four patients and a proton pump inhibitor in 24.

Results Twenty-one patients have completed treatment, with macroscopic replacement of the columnar lining by squamous epithelium, and have been followed for a median of 4 (range 3–12) months. Four patients are still in treatment and one patient has withdrawn from the study. Two oesophageal perforations, with one death of a patient with high-grade dysplasia who was unfit for oesophageal resection, occurred early in the study. Histological confirmation of squamous replacement has been sought, and found in 12 patients to date. In five patients, the squamous lining was associated with nests of underlying intestinal metaplasia. Standard doses of proton pump inhibitor were insufficient to control acid reflux in four patients, and needed to be increased.

Conclusion ABPC, in conjunction with adequate control of gastro-oesophageal reflux, allows squamous regrowth in both benign and dysplastic Barrett's oesophagus. Despite theoretical safety advantages of ABPC over techniques such as laser, oesophageal perforation may occur with this technique. The significance of foci of intestinal metaplasia underneath normal squamous epithelium is not yet clear. ABPC in 'uncomplicated' Barrett's oesophagus cannot yet be recommended until long-term follow-up of a cohort of cases so treated is able to show a decreased incidence of, and mortality rate associated with, adenocarcinoma.

Angiogenesis as a marker of recurrence in rectal carcinoma

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Background Angiogenesis is important in the development and spread of malignant tumours. The aim of this study was to investigate the significance of tumour microvascular density (MVD) in the recurrence of rectal carcinoma following curative surgery.

Methods Sections (4 μm) stained with antifactor VIII antibody were obtained from tumour blocks from the resection specimens of 31 patients who had undergone 'curative' resection of rectal carcinoma and developed tumour recurrence and of 24 patients who remained tumour free 5 years after surgery. Antifactor VIII antibody stains endothelial cells and allows identification of blood vessels. Microvessel counts at the invading tumour edge were made in six 200× fields (20× objective and 10× ocular) by two independent observers.

Results MVD increased with tumour stage. Across the stages in the no-recurrence group, there was a significant increase in MVD from Dukes A to C ($P<0·05$). This difference between Dukes A and C tumours was lost in the recurrence group ($P<0·32$). Overall, MVD was significantly higher in patients developing recurrence.

	Microvascular density			
	No recurrence	Recurrence	P*	P†
Overall	24·5(6·4)	30·7(9·3)	0·007	0·0007
Dukes A ($n=9$)	19·6(3·7)	27·5(4·9)	0·026	0·078
Dukes B ($n=21$)	25·3(6·7)	27·5(5·3)	0·42	0·30
Dukes C ($n=25$)	26·3(6·3)	33·7(11·4)	0·088	0·004

Values are mean(s.d.). *Unpaired t test; †paired t test

Conclusion This study demonstrates that MVD increases with tumour stage and is a significant marker of tumour recurrence. The behaviour of Dukes A tumours above a certain MVD begins to parallel that of Dukes C tumours in terms of recurrence.

Isolation of novel antibodies to colorectal tumour markers using a bacteriophage-display library

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Background Bacteriophage-display technology can be used to isolate antibody specificities to both immunogenic and non-immunogenic antigens in their native state. Potentially, antibodies to novel, highly specific, colorectal tumour-associated antigens could be isolated by probing the tumour cell surface with a phage-display library.

Methods A whole cell-based panning technique to generate colorectal tumour-specific antibodies is described. The synthetic Nissim antibody phage-display library was individually panned against two colorectal tumour cell lines, HT29 and LoVo. Following the initial panning, the library was immediately panned against a breast carcinoma cell line (T47D) to remove specificities reacting with common antigens. Two further rounds of panning against the individual colorectal cell lines were conducted. Whole cell enzyme-linked immunosorbent assay was used to select individual clones showing high absorbance with the colorectal cell line and low absorbance with T47D. These results were confirmed by fully automated cell-count system (FACS) analysis.

Results

	Absorbance (A_{405}–A_{690})		FACS (% positive staining)	
Clone	HT29	T47D	HT29	T47D
AF8	0·544	0·003	47·1	6·2
AF11	0·549	0·008	25·3	6·9
BC9	0·586	0·032	75·4	6·7

Further FACS analysis with a panel of six colorectal and three breast cell lines confirmed colorectal-specific and cell line-specific clones. Interestingly, none of these cell line-specific clones binds primary colorectal tumour sections from snap-frozen tissue.

Conclusion Having developed a successful whole cell-based panning method it is intended to repeat this procedure using primary colorectal tumour cells.

Regulation of matrix metalloproteinase (MMP)2 and its activator membrane-type MMP in colorectal cancer

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Background Amongst the broad family of matrix metalloproteinases (MMPs), MMP-2 plays an important role in the degradation of the basement membrane. The membrane-type MMP (MT-MMP) is the sole activator of pro-MMP-2 and is believed to be liberated by cancer cells. The nature of interaction between the colonic cancer cells and fibroblasts which brings this about was explored by co-culturing the two cell lines.

Methods The fibroblast cell line KB16F and colonic cancer cell lines HT115 and HRT18 were grown in separate flasks. Some 0·6 million tumour cells were added to the fibroblasts and incubated. In the second experiment, the conditioned medium from a cancer cell line was added to the fibroblast cell line and the cells were incubated for a similar duration. Both the experiments were performed for 72 h, at the end of which the conditioned medium was subjected to standard sodium dodecyl sulphate–polyacrylamide gel electrophoresis gelatin zymography. The lytic bands were sized against standard markers and MMP-2 was identified. The cells were subsequently scraped off and subjected to Northern blot analysis and probed with complementary DNA probes of MMP-2 and MT-MMP.

Results The fibroblasts constitutively expressed pro-MMP-2 and active MMP-2 while the colonic cell lines did not produce any MMP. Northern blot analysis revealed MMP-2 and MT-MMP RNA in fibroblasts only. On co-culture, and also when the fibroblasts were exposed to tumour-conditioned medium, there was an increased activation of pro-MMP-2. This was associated with translational upregulation of MMP-2 and MT-MMP messenger RNA (mRNA) in the fibroblasts.

Conclusion These data suggest that expression of fibroblast MMP-2 is under translational regulation and is intimately associated with MT-MMP mRNA expression. This co-expression of MMP-2 and MT-MMP in fibroblasts questions the popular belief that MT-MMP is expressed solely by cancer cells.

Loss of perivascular nerves in the submucosa adjacent to colorectal cancer

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Background Various cancers lack perivascular innervation. However, blood vessel innervation has been observed in tissue adjacent to tumours, but no quantitative study exists.

Methods The perivascular innervation of arterioles in colorectal cancer ($n = 15$) and adjacent submucosa was studied using a panel of immunohistochemical markers of transmitters: neuropeptide Y (NPY), tyrosine hydroxylase (TH), vasoactive intestinal peptide (VIP), substance P (SP) and calcitonin gene-related peptide (CGRP). Immunoreactivity was compared with that of normal colonic tissue (controls). Furthermore, distance from the tumour edge over which immunoreactivity was reduced was measured.

Results The absence of perivascular nerves within colorectal cancers was confirmed, and in addition loss of perivascular nerves in areas of submucosa adjacent to cancers was noted. The loss was progressively greater with advancing tumour stage (Dukes A to C) for TH, NPY and VIP. The pattern of loss varied for different transmitters: in the submucosa of Dukes A cancers, a mean 5 per cent of the total number of arterioles showed TM immunoreactivity (controls, 75 per cent), 69 per cent showed NPY immunoreactivity (controls, 95 per cent) and 23 per cent showed VIP immunoreactivity (controls, 57 per cent). For Dukes B submucosal arterioles, immunoreactivity dropped to 7, 12 and 20 per cent and for Dukes B to 0, 9 and 17 per cent (TH, NPY and VIP respectively). There was no decrease in SP in Dukes A submucosa (40 per cent) compared with controls, but immunoreactivity fell in Dukes B (19 per cent) and C (0 per cent). CGRP immunoreactivity was never above 4 per cent. Reduced NPY immunoreactivity was observed over a mean of 4·3 mm (Dukes A/B, 1·3 mm; Dukes C/D, 5·7 mm) and 4·5 mm for VIP (Dukes A/B, 3·9 mm; Dukes C/D, 6·0 mm). TH and SP measurements did not return to normal within the available tissue (8·3 mm).

Conclusion There exists a progressive loss of neurotransmitters with stage. This suggests the tumour itself may influence neural integrity, perhaps via the secretion of humoral factors.

Colorectal cancer vaccine 105AD7 increases tumour infiltration of CD25-positive lymphocytes

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Background The anti-idiotypic monoclonal antibody 105AD7 mimics an antigen present on 80 per cent of colorectal cancer cells. Phase I studies have confirmed that the vaccine is non-toxic. Work previously presented to the Society has shown increased expression of the interleukin 2 receptor, CD25, on immunohistochemical staining of tumour sections from patients receiving the vaccine before surgery. The aim of this work was to assess expression of the activation markers CD25, human leucocyte antigen (HLA) DR and CD69 on lymphocytes at the tumour site of patients with colorectal cancer receiving 105AD7, and their controls, using flow cytometry.

Methods Tumour samples were taken prospectively from the resection specimens of 54 patients. Nineteen patients had received 105AD7 before surgery, while 35 had not. Samples were disaggregated with collagenase/DNAase and lymphocytes were separated out using a discontinuous Percoll gradient. Lymphocyte preparations were labelled with CD3, CD4, CD25, HLA-DR and CD69 and analysed blindly on the FACScan.

Results Results were available for 16 of 19 immunized patients and 26 of 35 controls. The percentage of lymphocytes expressing CD25 was higher in patients receiving 105AD7 before operation (8 *versus* 4 per cent; $P = 0{\cdot}003$), as was expression of CD3/CD69 (66 *versus* 58 per cent; P not significant) and CD4/HLA-DR (26 *versus* 23 per cent; P not significant).

Conclusion Increased expression of CD25 at the tumour site of patients who received 105AD7 suggests a population of activated lymphocytes and confirms results obtained using immunohistochemistry. This may confer a survival advantage on patients who receive the vaccine. Further work needs to be done.

Relationship between circulating tumour cell cluster prevalence and stage in colorectal cancer

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Background The authors have previously demonstrated that reverse transcriptase–polymerase chain reaction (RT–PCR) can be used to identify complementary DNA (cDNA) coding for carcinoembryonic antigen (CEA) in the circulation of patients with colorectal cancer, and that multiple blood sampling increases the probability of detecting a cancer cell cluster. Possible differences in cell cluster prevalence between primary and metastatic or node-negative and node-positive primary cancer have been examined.

Methods Some 14 ml peripheral venous blood were sampled via a cannula from patients with colorectal cancer, after discarding the first 5 ml, three times at 1-min intervals. After the addition of erythrocyte lysis buffer, total RNA was extracted by conventional methods from the remaining cells and subjected to RT–PCR

using specific primers for cDNA CEA (29 cycles). The PCR products were run on electrophoresis gels. The PCR product was confirmed by Southern blotting using an oligoprobe which lies between the two primers. Forty-three patients without known carcinoma used as controls were all found to be negative.
Results There was a significant increase ($P < 0{\cdot}05$, Fisher's exact test) in RT–PCR positivity of metastatic (24 of 27) compared with primary (17 of 26) tumour samples, but no significant difference between Dukes A and B (11 of 16) compared with C (six of ten) primary tumour samples. Similarly there was a significant increase ($P < 0{\cdot}05$, Kendall's tau test) in cell cluster prevalence of metastatic (median 2 (interquartile range 1–3)) compared with primary (1 (0–2)) tumour samples, but no significant difference between Dukes A and B (1 (0–2)) compared with C (1 (0–3)) lesions.
Conclusion The increase in cell cluster positivity and prevalence in metastatic but not in node-positive primary carcinoma suggests that the presence of circulating cancer cells may relate to factors other than biological behaviour, such as tumour bulk and hepatic portal filtration.

Genotoxicity of 5-aminolaevulinic acid

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Background 5-Aminolaevulinic acid (ALA) is a prodrug for the fluorescent photosensitizer protoporphyrin IX (PpIX) used for diagnosis and treatment of epithelial tumours. PpIX interacts with light to induce photodynamic tissue damage including DNA damage. However, there have been recent reports of ALA-induced DNA damage in the absence of light. This is of concern in the diagnostic use of ALA in otherwise healthy individuals and has been evaluated in an *in vitro* cell culture model and an *ex vivo* clinical model.
Methods MCF7 cells were incubated in ALA 0–1 mmol l^{-1} for 5 h in the dark. Cells were disaggregated and single-cell gel electrophoresis (comet assay) was performed to determine the extent of DNA damage. Oesophageal and gastric biopsies from ALA-sensitized patients were similarly disaggregated and the comet assay performed.
Results The extent of DNA damage in MCF7 cells was statistically significant at ALA 1 mmol l^{-1} compared with control ($P < 0{\cdot}001$). At ALA 1 mmol l^{-1}, the mean(s.d.) damaged DNA content was 7·0(0·3) per cent compared with 3·2(0·1) per cent in the absence of ALA (negative control), and 26·6(0·5) per cent in the presence of ALA plus light (positive control). The damaged DNA content in mucosal biopsies was 3·5(0·2) per cent in controls and 3·4(0·3) per cent for patients pretreated with ALA 20 mg kg^{-1} ($P = 0{\cdot}3$).
Conclusion ALA causes a dose-dependent dark genotoxicity in cell culture. However, DNA damage was not detected in biopsies from patients receiving a clinically relevant dose of ALA 20 mg kg^{-1}. The result of this study lends support to the continued clinical use of ALA.

Increasing primary tumour vascularity and proliferation does not increase metastasis

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Background Primary tumour vascularity has been shown to correlate with metastasis. The effect of growth factor-induced change in primary tumour vascularity and proliferation on metastasis has been examined.
Methods The spontaneously metastasizing rat tumour K12/TR which proliferates in response to basic fibroblast growth factor (bFGF) was used. K12/TR tumour cells (10^6) were injected subcutaneously into BDIX rats and infused continuously for 28 days with bFGF or saline using an osmotic minipump, and the resulting subcutaneous tumour was then excised. Tumour sections were stained for vascularity (OX-43 antibody) and proliferation (PC10 antibody). Vessel volume, vessel count and proliferation index were determined at ×400 magnification by graticule counting. Blood flow was determined by the autoradiographic ratio of $[^{125}I]$iodoantipyrine activity between the tumour edge and centre. After a further 2 months the animals were killed and the lungs examined for metastases.
Results

	Saline	bFGF	*P*
Primary tumour			
Vessel volume (%)	3·6 (2·5–4·3)	5·9 (5·8–6·2)	0·004
Vessel count (mm^{-2})	35 (34–36)	65 (62–77)	0·008
Blood flow (central tumour : tumour edge ratio)	0·3 (0·3–0·3)	1·1 (0·9–1·2)	0·05
Proliferation index (%)	12 (9–15)	21 (20–23)	0·03
Tumour volume (ml)	1·1 (1·1–1·8)	2·5 (2·1–2·6)	0·02
Lung metastases	9 of 17	11 of 18	0·3

Conclusion An increase in primary tumour vascularity and proliferation was not associated with increased metastasis. The results suggest that metastasis was limited by factors other than primary tumour proliferation and vascularity.

Value of colonoscopic biopsies for genetic analysis

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Background Patients with hereditary non-polyposis colorectal cancer (HNPCC) have inherited mutations in one of the DNA mismatch repair genes. These individuals develop cancers that generally show microsatellite instability and are prone to synchronous and metachronous colorectal cancers as well as extracolonic cancers. Identification of the precise germline mutation demands screening several genes. However, microsatellite instability status is a useful marker for a defective mismatch repair system and may be of relevance in families that do not conform with the clinical criteria for HNPCC. Microsatellite instability is also a feature of patients at risk of metachronous colorectal cancers. Preoperative knowledge of the genetic abnormality may therefore influence surgical treatment. This study investigated the adequacy of colonoscopic biopsy in genetic analysis.
Methods Six specimens were taken with a colonoscopy forceps and larger tissue specimens were obtained from 13 resected cancers and two villous adenomas, and examined for microsatellite instability at D2S123, D18S58, BAT25, BAT26 and BAT40 by single-stranded conformational polymorphism analysis. Codons 1264–492 of the *APC* gene were also investigated for mutations.
Results None of these tumours showed microsatellite instability. However, the banding patterns of the colonoscopic biopsies and those available from resected specimens were completely consistent for each patient. A somatic mutation of the *APC* gene was detected in all the specimens taken from one tumour.
Conclusion These results suggest that colonoscopic biopsies are sufficiently reliable in defining the genetic make-up of individual colorectal tumours for this investigation to be employed in management.

Expression of cadherin–catenin complex in premalignant gastric mucosal lesions

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Background E-cadherin, β-catenin and α-catenin are normally found at the cell membrane, forming the basis of intercellular adherens junctions. Weak membranous or strong cytoplasmic

expression of these proteins is therefore abnormal, and can occur in gastric cancer. The aim of this study was to determine cadherin and catenin expression in premalignant gastric mucosal lesions.
Methods Paraffin-embedded material from endoscopic biopsies showing dysplasia ($n = 17$), intestinal metaplasia (IM, $n = 17$) or chronic atrophic gastritis (CAG, $n = 25$) were stained for E-cadherin, and α- and β-catenins by immunohistochemical methods and compared with 20 histologically normal biopsies.
Results Abnormal expression of the three proteins was noted as shown in the *Table*.

Expression	Dysplasia	IM	CAG	Normal
E-cadherin (cytoplasmic)				
Strong	12†	7*	0	0
Weak or negative	5	7	25	20
E-cadherin (membranous)				
Strong	9	13	25	20
Weak or negative	8*	1	0	0
α-catenin (cytoplasmic)				
Strong	11†	3	0	0
Weak or negative	5	8	25	20

$^*P<0{\cdot}02$, $^†P<0{\cdot}001$ (χ^2 test with Yates' and Bonferroni correction)

Both dysplasia and IM showed significant cytoplasmic expression of E-cadherin; dysplasia also showed significant cytoplasmic expression of α-catenin and reduced membranous E-cadherin expression.
Conclusion Abnormal expression of E-cadherin and α-catenin increases with increasingly severe premalignant change in gastric mucosa. Further studies are warranted to determine whether these changes define a subset at higher risk of malignant change.

Non-invasive technique to assess hepatic tissue oxygenation using near-infrared spectroscopy

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Background Adequate hepatic tissue oxygenation is vital to the outcome of liver surgery and transplantation. Near-infrared spectroscopy (NIRS) is a non-invasive method for measurement of tissue oxygenation. The aim of this study was to validate NIRS for measurement of hepatic tissue oxygenation.
Methods The study was conducted under a licence granted by the Home Office in accordance with the Animals (Scientific Procedures) Act 1986. Large Landrace pigs ($n = 11$) underwent laparotomy. Hepatic blood flow measurement was done by ultrasonic probes placed around portal vein (PV) and hepatic artery (HA). NIRS was recording continuously oxyhaemoglobin (HbO$_2$), deoxyhaemoglobin (Hb), total haemoglobin (HbT) and differential haemoglobin (HbD). Hepatic vascular inflow occlusion (HVIO) was done in six animals. Reduction of the inspired oxygen fraction ($F_{\mathrm{iO_2}}$) was done in five animals.
Results NIRS measurements with HVIO are shown in the *Table*.

	HA occlusion	PV occlusion	HA and PV occlusion
Hb (μmol l^{-1})	9·2(20·6)	16·0 (55·2)	37·7(109·6)
HbO$_2$ (μmol l^{-1})*	− 49·7(19·6)	− 124·8(55·1)	− 197·2(59·2)
CyOx (μmol l^{-1})*	8·7(6·1)	23·4(9·5)	35·2(8·8)
HbD (μmol l^{-1})*	− 58·8(32·6)	− 140·8(48·1)	− 234·9(103·2)
HbT (μmol l^{-1})†	− 40·5(23·6)	− 108·8(99·2)	− 159·5(142·8)

Values are mean(s.d.) for six pigs. $^*P<0{\cdot}01$, $^†P<0{\cdot}05$ *versus* baseline

A significant correlation was found between the reduction of hepatic blood flow and hepatic HbO$_2$ ($r = 0{\cdot}68$, $P<0{\cdot}05$). With reduction of the $F_{\mathrm{iO_2}}$, a significant correlation was found between HbO$_2$ and Hb and arterial oxygen saturation ($r = 0{\cdot}82$ and $r = -0{\cdot}88$ respectively, $P<0{\cdot}01$).
Conclusion NIRS can be used as a non-invasive method for assessing hepatic tissue oxygenation.

Colonic cancer cell-mediated upregulation of fibroblast-derived matrix metalloproteinase 9 is dependent on a cancer cell membrane component

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Background Matrix metalloproteinases (MMPs), which are capable of degrading extracellular matrix, are implicated in tumour invasion and metastasis. Among the broad family of metalloproteinases, MMP-9 has been strongly implicated in the invasion of colonic cancers. Stromal fibroblasts are the principal cells that release MMP-9. The interaction between colonic cancer cells and fibroblasts which upregulates MMP-9 expression was clarified by co-culturing human colonic cancer cells and fibroblasts.
Methods The fibroblast cell line KB16F and colonic cancer cell lines HT115 and HRT18 were grown in separate flasks. Some 0·6 million tumour cells were added to each fibroblast cell type and incubated in serum-free medium. Subsequently, the conditioned medium from the cancer cell line was added to the fibroblast cell lines. In a third experiment, the cells were incubated in tissue culture inserts separated by a 3-μm porous filter which prevents physical contact between the cells but allows chemicals to diffuse freely. Finally, the tumour cells were methanol fixed and co-cultured with fibroblasts. All the experiments were conducted for 72 h, at the end of which the conditioned medium was subjected to standard sodium dodecyl sulphate–polyacrylamide gel electrophoresis gelatin zymography. The lytic bands were sized against standard markers and MMP-9 was identified.
Results The fibroblast cell line and colonic cell line did not produce any MMP-9 under basal conditions. There was an increased expression of fibroblast MMP-9 only when the cells were co-cultured and this was also evident when the tumour cells were methanol fixed. MMP-9 failed to appear when the fibroblasts were exposed to tumour-conditioned medium and also when the cells were incubated in tissue culture inserts.
Conclusion These data suggest that colonic cancer cell-mediated upregulation of fibroblast MMP-9 is due to a cancer cell membrane component.

Influence of intra-abdominal bleeding on peritoneal fibrinolysis and adhesion formation

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Background Intraoperative bleeding potentially promotes adhesion formation because of the presence of increased fibrin deposition between tissue surfaces. The effect of controlled blood loss to the peritoneal cavity was investigated to determine its effect on peritoneal fibrinolysis and adhesion formation following laparoscopic and open bowel manipulation.
Methods Sixty-five male Sprague–Dawley rats were divided to diagnostic laparoscopy (lap) and laparotomy (open), and baseline control groups. Controlled blood loss was simulated by tail-vein venesection of 1·5 ml blood which was evenly injected into the peritoneal cavity. Controls received 1·5 ml saline. Systematic bowel handling and inspection of the peritoneal cavity

was performed in all animals with instruments only. Five rats from each group were killed at 2 and 4 days, and at 2 weeks. Intra-abdominal adhesion scores were measured. Peritoneal fibrinolysis was assessed from samples of parietal peritoneum by measurement of plasminogen activator (PAA) and inhibitor (PAI) activity.

Results

		2 days			
	Baseline	Open + blood	Lap + blood	Open + saline	Lap + saline
PAA (×10^2 units ml^{-1})	13·0(1·0)	32·0(7·0)*	31·0(11·0)*†	32·0(15·0)*	24·0(6·0)*
PAI (units ml^{-1})	12·0(7·7)	7·6(5·7)	9·5(6·1)	7·5(5·8)	10·1(7·[illegible])
Adhesion score	0	0·8(0·4)	1·0(0·7)	0	0·4(0·8)

		4 days			
	Baseline	Open + blood	Lap + blood	Open + saline	Lap + saline
PAA (×10^2 units ml^{-1})	13·0(1·0)	45·0(39·0)*	33·0(11·0)*†	36·0(13·0)*†	28·0(8·0)*
PAI (units ml^{-1})	12·0(7·7)	10·6(5·7)	10·0(3·2)	9·6(5·2)	9·3(3·4)
Adhesion score	0	2·0(0·7)	0·2(0·2)	0·2(0·2)	0·4(0·4)

		2 weeks			
	Baseline	Open + blood	Lap + blood	Open + saline	Lap + saline
PAA (×10^2 units ml^{-1})	13·0(1·0)	22·0(8·0)	16·0(2·0)	17·0(4·0)	17·0(3·0)
PAI (units ml^{-1})	12·0(7·7)	3·8(7·7)	5·2(7·8)	5·3(8·0)	6·8(5·4)
Adhesion score	0	8·4(3·4)	1·6(2·0)‡	2·4(2·0)‡	0·8(1·0)‡

Values are mean(s.d.). *$P < 0·05$ *versus* control, †$P < 0·05$ *versus* 2 weeks (Kruskal–Wallis test); ‡$P < 0·001$ *versus* 2 weeks open + blood (Tukey–Kramer multiple comparisons)

Surgery resulted in a universal rise in PAA at 2 and 4 days which returned to normal at 2 weeks. There was, however, no change in PAI activity. At 2 weeks blood in the peritoneum was associated with a significantly greater adhesion score compared with that in controls which received saline. Moreover, intraperitoneal bleeding during laparotomy resulted in a significantly greater adhesion score than laparoscopy.

Conclusion The presence of blood in the peritoneum in combination with laparotomy synergistically enhances the formation of postoperative adhesions.

Heme oxygenase 1: a potential marker of surgical stress

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Background Laparoscopic surgery provides distinct clinical advantages for the patient, yet whether or not it is metabolically less 'stressful' than open surgery remains controversial. Heme oxygenase 1 (HO-1) is a highly inducible stress protein, responsible for the catabolism of cellular heme to biliverdin (a powerful antioxidant) and as a consequence protects the cell from further insult. The aim of this study was to determine if surgical stress induces atrial HO-1 messenger RNA (mRNA) expression and whether the degree of gene expression reflects the apparent difference in 'stress' between laparoscopic and open surgery.

Methods Male Sprague–Dawley rats (weight 400–550 g) were randomized to anaesthetic only, 1 h of carbon dioxide pneumoperitoneum (intra-abdominal pressure 8–10 mmHg) or 1 h laparotomy. The animals were killed and both atria isolated for RNA extraction. Differential reverse transcription–polymerase chain reaction (using β-actin as internal standard) was used to detect and semiquantify the HO-1 mRNA present in 1 μg extracted RNA. The results are expressed as a ratio of the amount of HO-1 mRNA to β-actin mRNA for each group.

Results

	HO-1/β-actin ratio
Control	1·42(0·06)
Pneumoperitoneum	1·45(0·07)
Laparotomy	2·11(0·25)*

Values are mean(s.e.m.) for each group ($n = 6$–7). *$P < 0·05$ *versus* control and pneumoperitoneum (Mann–Whitney U test)

Conclusion Atrial HO-1 expression increased significantly during open surgery, but not during pneumoperitoneum. HO-1 induction may be important in differentiating the degree of surgical stress associated with a particular operative approach.

Rat liver preservation with phosphate-buffered sucrose: demonstration in an isolated perfused liver model

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Background Phosphate-buffered sucrose (PBS140) is a clinically proven and inexpensive kidney preservation solution but it has not been fully evaluated in liver preservation. Successful liver preservation for 24 h with PBC140 in a model of isolated perfused rat liver is reported with results comparable to those obtained with University of Wisconsin solution (UW).

Methods Wistar rats (200–250 g) were anaesthetized with intraperitoneal pentobarbitone 50 mg kg^{-1}. After a midline laparotomy, the common bile duct was cannulated with a fine-bore polyethylene catheter. Some 50 units heparin in 2 ml normal saline were injected via the penile vein. The aorta was cannulated and the liver flushed *in situ* with 20 ml Ringer lactate (control), UW or PBS140. Some 5 ml test solution was next perfused via the portal vein. The liver was removed and stored in the flush solution at 40°C. After 24 h of storage, the liver was set up on a recirculating circuit system at 37°C. The basic solution for reperfusion was Ringer lactate to which bovine red cells were added to increase the oxygen carrying capacity and bovine albumin to maintain the oncotic pressure. Taurocholic acid (4·84 per cent) was infused at 5 ml h^{-1} to the inflow system to support bile production. Bile was collected during the reperfusion period. Lactate dehydrogenase (LDH), aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) levels were determined after preservation and reperfusion. The concentration of bilirubin in the bile was also measured and the percentage of bile acid used by the liver was calculated.

Results

Test solution	Bile flow (μl per 2 h per g)	Bile acid used in the liver (%)	Bilirubin (mg dl^{-1})	Enzyme (units l^{-1}) ALAT	ASAT	LDH
UW	145(7)	55·2(3·4)	4·41(0·49)	17·0(0·3)*	23·2(5·4)*	179·6(20·4)*
(n = 6)				24·3(1·1)†	30·2(3·5)†	83·5(8·3)†
PBS140	147(16)	50·8(4·5)	6·65(0·74)	33·3(2·8)*	30·1(3·5)*	161·4(15·5)*
(n = 8)				43·9(3·3)†	62·2(5·5)†	181·3(15·6)†
Ringer lactate	45(7)	8·3(2·8)	1·55(0·36)	170·9(29·4)*	224·8(36·3)*	1640·1(132·1)*
(n = 6)				118·2(19·4)†	331·5(34·4)†	1107·4(181·8)†

Values are mean(s.e.m.). *After preservation for 24 h (first flush); †after reperfusion (last flush)

Conclusion These results suggest that PBS140 is worthy of further investigation for preservation of organs other than kidney.

Novel human model of intestinal epithelial regeneration

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Background Intestinal epithelial regeneration is central to inflammatory, ulcerative and infective diseases of the intestine, but regulatory mechanisms are obscure. Lack of a suitable model has hampered progress. This study aimed to develop a reproducible model of human intestinal epithelial regeneration.
Methods Human fetal intestinal epithelium at 10–16 weeks' gestational age was retrieved, diced and washed. The epithelial layer was disaggregated by collagenase and dispase, then differentially centrifuged to obtain homogeneous preparations of crypt progenitor epithelium. Epithelial preparations were cultured *in vitro* and grafted subcutaneously (20 μl per graft) to Scid (severe combined immunodeficient) mice. Grafts were retrieved at intervals of 7, 14, 21, 35 and 50 days after transplantation for assessment of morphology and differentiation.
Results Twenty-one of 26 grafts were successful. A temporal sequence of regeneration was shown: by 7 days the epithelium formed an undifferentiated proliferative mass ('blastema' stage), by 21 days there was crypt formation, by 35 days crypt fission and by 50 days cytodifferentiation and villus formation. Cultured cells expressed epithelial markers cytokeratins 8 and 18.
Conclusion This study has developed the first model of human intestinal epithelial regeneration, which may be applied to studies of inflammatory bowel disease.

Effect of malnutrition on gut permeability and septic outcome following major surgery

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Background Malnutrition in hospitalized patients is prevalent and is associated with an enhanced risk of developing sepsis. Failure of gut barrier function with resultant translocation of bacteria and endotoxin has been incriminated in the pathogenesis of the sepsis response. The relationship between the degree of malnutrition, intestinal permeability and incidence of septic events was investigated in 56 patients undergoing major resectional surgery for oesophageal, gastric and pancreatic cancer.
Methods Preoperative nutritional status was assessed by Nutritional Risk Index (NRI = (1·519 × serum albumin) + 0·417 × (current weight/usual weight) × 100) in all patients. Intestinal permeability (lactulose : mannitol (L : M) ratio) and serum immunoglobulin (Ig) M antiendotoxin (EndoCAb) antibodies were determined before operation (PRE) and on postoperative days 1 and 7 (POD1 and POD7). Thirty-day septic morbidity (intra-abdominal abscess/empyema and pneumonia) was recorded.
Results Degree of malnutrition, intestinal permeability, endotoxin levels and incidence of sepsis are shown in the *Table*.

Degree of malnutrition	L : M ratio PRE	POD1	POD7	IgM EndoCAb (MU ml^{-1}) PRE	POD1	POD7	Sepsis (%)
Well nourished NRI > 97·5 (n = 21)	0·05(0·1)	0·18(0·9)	0·09(0·1)	161(189)	92(97)	235(161)	14
Mildly malnourished NRI 83·5–97·5 (n = 26)	0·09(0·9)	0·19(3·2)	0·08(0·5)	152(67)	83(52)	210(151)	30
Severely malnourished NRI < 83·5 (n = 9)	0·07(0·3)	0·15(0·1)	0·21(0·4)	134(127)	96(45)	223(172)	44

Values are median(s.d.)

Logistic regression analysis did not identify significant association between intestinal permeability, level of endotoxin and the development of sepsis.
Conclusion These data confirm that severely malnourished patients have a higher incidence of sepsis following major resectional surgery compared with non-malnourished patients. Although permeability in the severe group remains raised 7 days after operation, there is no association between the degree of malnutrition and intestinal permeability following major surgery, and thus no clear link with failure of gut barrier function and septic outcome in malnourished patients.

Direct acidification of colonic mucosa by dopamine via D_{1A} receptors

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Background Tonometric measurements of colonic and gastric mucosal pH are used to determine splanchnic perfusion. Acidification is assumed to signify poor circulatory responses to dopamine. Colonic mucosa was probed for dopamine receptor subclasses and direct effects of dopamine on cellular pH (independent of oxygenation) were examined.
Methods Receptor subclasses were co-localized with immunohistochemistry and *in situ* hybridization. Cellular pH was recorded using confocal laser imaging of mucosal crypts from the distal colon of adult Sprague–Dawley rats. Crypts were loaded with a pH-sensitive fluorescent probe and perfused with Ringer's solution. Fluorescent emission intensity was expressed as mean(s.e.m.) percentage of the basal value at a dose of 250 nmol l^{-1} for n = 144 (n = number of cells measured per crypt × number of crypts × number of animals). A t test was used for statistical analysis. Ethics committee approval was obtained.
Results D_{1A} receptors were localized to mucosal crypts. Dopamine perfusion produced a cytosolic acidification within a mean(s.e.m.) of 2(0·4) min (47(12) per cent). The action of dopamine was unaffected by: (1) the absence of bicarbonate (acetazolamide and carbon dioxide-free perfusion) (46(6) per cent); (2) α/β-adrenergic receptor blockade (prazosin and propranolol respectively) (48(14) per cent); or (3) protein kinase C inhibition with chelerythrine (49(9) per cent) (all $P > 0·8$). No effect of dopamine was seen following acidification by adenosine 3',5'-cyclic monophosphate (cAMP) with forskolin or by sodium–proton exchange inhibition with ethylisopropylamiloride (both $P > 0·8$).
Conclusion Dopamine directly acidifies mucosal crypt cells by inhibiting sodium–proton exchange via cAMP-mediated D_{1A} receptors. This would account for previously unexplained

mucosal acidification during low-dose dopamine infusion. Direct effects of pharmacological agents on mucosal tissue must be taken into account when evaluating perfusion parameters based on tonometric data.

Visceral ischaemia is associated with systemic fibrinolysis in major aortic aneurysm surgery

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Background Haemorrhagic problems are a common and potentially fatal complication following aneurysm surgery. The fibrinolytic system was investigated during elective thoracoabdominal aneurysm (TAA) and infrarenal aneurysm (AAA) surgery.

Methods Fifteen patients with TAA and 13 with AAA were studied. Tissue-type plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1) antigen levels were measured in arterial plasma collected at incision, aortic clamping, immediately on reperfusion and 15, 60 and 180 min thereafter. Data are presented as median (interquartile range) and analysed using non-parametric tests (Wilcoxon or Mann–Whitney *U* test).

Results At incision patients with AAA had a higher baseline level of tPA than those with TAA ($P = 0{\cdot}003$). In both groups levels rose during the procedure and were always significantly higher than the initial value ($P < 0{\cdot}01$ at all time points). However, the rise on reperfusion was approximately three times greater in patients with TAA (36·4 (14·8–69·3) ng ml^{-1}) than in those with AAA (10·6 (7·6–11·9) ng ml^{-1}) ($P = 0{\cdot}002$). By 60 min after reperfusion, values were similar in both groups. Baseline PAI-1 levels were also similar in both groups. PAI-1 concentration showed a progressive and significant rise above baseline in both groups at all time points ($P < 0{\cdot}005$); however, there were no significant differences between the two groups at these times.

Conclusion tPA and PAI-1 activity is significantly increased in aneurysm surgery. Prophylactic administration of antifibrinolytic agents may be useful, especially when supracoeliac clamping is required.

Novel technique of perioperative leucodepletion: effect on cell counts and neutrophil activation

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Background Polymorphonuclear neutrophils (PMNs) are integral to the pathogenesis of ischaemia–reperfusion injury (IRI) and PMN depletion by both mechanical and immunological methods has been shown to ameliorate this injury in animal models. However, a clinical assessment of such techniques has not been performed.

Methods In ten patients undergoing limb salvage surgery the effect of PMN depletion (using a double-lumen femoral venous catheter, extracorporeal circuit, leucocyte filter, and flow rates of 200 ml min^{-1} for 15 min (3000 ml or approximately 60 per cent blood volume filtered)) on PMN, monocyte and lymphocyte counts, adhesion molecule expression (CD11b, CD18, L-selectin) and myeloperoxidase (MPO) levels was compared with changes in ten control patients undergoing similar surgery. Samples were taken from both peripheral (PER) and femoral (FEM) venous blood at baseline and at reperfusion, 4 h, 24 h, 3 and 6 days (T_0, T_4, T_{24}, T_{3D} and T_{6D} respectively).

Results PMNs were effectively depleted from the filtered blood from a median (interquartile range) of 4·04 (2·55–5·75) to 0·72 (0·42–1·30) $\times 10^9$ l^{-1} ($P = 0{\cdot}002$) and 1·08 (0·10–1·89) $\times 10^9$ l^{-1} ($P = 0{\cdot}012$) following 5 and 15 min of filtration respectively. Monocyte counts also fell from 0·30 (0·20–0·46) to 0·03 (0–0·20) $\times 10^9$ l^{-1} ($P = 0{\cdot}004$) at 5 min and 0·8 (0·03–0·10) $\times 10^9$ l^{-1} ($P = 0{\cdot}09$) at 15 min. Similar lymphocyte counts were reduced from 1·45 (1·09–1·9) to 0·1 (0·08–0·22) $\times 10^9$ l^{-1} at 5 min and 0·95 (0·58–1·3) $\times 10^9$ l^{-1} at 15 min ($P < 0{\cdot}0001$ at both points). PMN adhesion molecule expression was always lower in filtered patients (both FEM and PER), and was significant for CD11b at T_0 FEM ($P < 0{\cdot}0001$), T_4 PER ($P = 0{\cdot}0195$), T_{24} FEM ($P = 0{\cdot}0012$) and T_{3D} ($P = 0{\cdot}0140$). The reduction in CD18 expression was significant at T_0 PER ($P < 0{\cdot}0001$) and T_{24} FEM ($P = 0{\cdot}0311$), and falls in L-selectin were significant at T_4 PER ($P = 0{\cdot}0072$). Levels of MPO were higher in the filter group at T_0 FEM ($P < 0{\cdot}0001$) and T_4 FEM ($P < 0{\cdot}0001$).

Conclusion This novel study of intraoperative PMN depletion shows a favourable level of diminished activated neutrophils, which may ameliorate IRI. The incidence of infective complications, amputation and death was comparable between the two groups. It has thus been demonstrated that in patients undergoing limb revascularization this technique is safe, and the results suggest that further investigation is warranted.

Postural effect on lower limb arterial blood flow: a diagnostic marker of clinical severity in peripheral vascular disease

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Background Lower limb arterial blood flow in normal subjects decreases as posture is altered from the horizontal to sitting position. This change, known as the venoarteriolar response (VAR), is due to local sympathetic axon reflex. Elevation of the lower limb venous pressure on dependency above a threshold level (pVAR) elicits the VAR, causing precapillary sphincters to contract and peripheral resistance to increase. The aim of the study was to determine whether the VAR and the pVAR are affected by peripheral vascular disease (PVD) in patients with intermittent claudication (IC) and whether they can be used as clinical markers for grading its severity.

Methods Eighty legs of normal volunteers (group 1) and 80 legs of patients with IC due to PVD (group 2) were included in the study. Two groups were matched for age and sex. Exclusion criteria were chronic cardiac failure, diabetes mellitus with peripheral neuropathy, chronic venous disease, leg oedema, collagen disease affecting the skin and use of nifedipine, all known to affect the VAR. Investigation entailed measurement of (1) maximal systolic ankle pressure (P_{ankle}), (2) resting (rABPI) and postexercise (peABPI) ankle:brachial pressure indices, (3) initial (pain free) (ICD) and absolute (ACD) claudication distances (treadmill 3·8 km h^{-1}, 10 per cent inclination) and (4) horizontal (HF) and sitting (SF) skin flow and the VAR (HF − SF/HF) obtained with laser Doppler fluxmetry on the dorsum of the foot. The ABPIs, P_{ankle}, VAR and pVAR were correlated with the ICD and ACD using linear regression.

Results

	VAR	pVAR (mmHg)	ICD (m)	ACD (m)	P_{ankle} (mmHg)
Group 1	0·59	45	—	—	145
Group 2	0·40	32	155	248	100
P*	< 0·05	< 0·05	—	—	< 0·05

Values are median. *Mann–Whitney *U* test

	Correlation coefficient				
	rABPI	peABPI	P_{ankle}	VAR	pVAR
ICD	0·36	0·33	0·2	0·62*	0·6*
ACD	0·39	0·33	0·23	0·65*	0·6*

$^*P<0{\cdot}02$

Conclusion The VAR and the venous pressure threshold that elicits it (pVAR) are significantly lower in claudicants than in normal subjects. The VAR and pVAR correlate significantly with the clinical severity of PVD, as determined by the ICD and ACD, yielding better correlation coefficients than the current clinical 'gold standard' of ABPI.

Aortic stent-graft incorporation and the inflammatory response to an endoprosthesis

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Background The incorporation of an endovascular stent-graft into the aorta of a pig was assessed and the inflammatory response to the endoprosthesis determined.

Methods Endoluminal stent-grafts were deployed into the infrarenal aortas of Large White pigs in accordance with Home Office Project Licence 30/01047. Animals were followed at intervals of up to 1 year. The aortas were explanted and specimens were subjected to gross observation, scanning electron microscopy (SEM) and light microscopy (LM).

Results Twenty-seven animals underwent infrarenal endoluminal stent-grafting. Four animals were excluded from follow-up because they had to be destroyed prematurely (aortic–stent-graft mismatch, acute stent-graft occlusion, iliac artery thrombosis, ear infection). The remainder were followed at 1 ($n=2$), 2 ($n=2$), 4 ($n=7$), 6 ($n=2$), 12 ($n=6$), 26 ($n=3$) and 52 ($n=1$) weeks. Macroscopically, an early neointima could be seen from week 4 and was well developed by week 12. SEM demonstrated intragraft thrombus at 1 week, with the development of a fibrin layer and islands of endothelial cells by week 2. A complete endothelial layer was seen at week 4. LM demonstrated a florid inflammatory reaction at 4 weeks, with lymphocytes and giant cells surrounding the graft. By 12 weeks the inflammation was marked by the presence of germinal centres. This response had largely subsided by 26 weeks and at 1 year only giant cells and a few lymphocytes persisted.

Conclusion In a porcine model, the aortic–stent-graft interface is well established by 4 weeks and complete by 12 weeks, by which time the stent-graft has a complete neointima. The initial acute inflammatory reaction seen at 4 weeks has become chronic by 12 weeks and is largely absent by 26 weeks after implantation.

Fast contrast-enhanced magnetic resonance angiography as a replacement for conventional digital subtraction angiography

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Background Digital subtraction angiography (DSA) is an invasive procedure with small but finite risks (vascular trauma, contrast reaction, radiation). Magnetic resonance angiography (MRA) avoids these problems although standard time-of-flight imaging is slow and may not differentiate between tight stenoses and occlusions. Thus a novel technique of MRA (gadolinium-enhanced contrast imaging: MRA-G) and a 'floating' table, as used for angiography, has been developed.

Methods Twenty patients (ten with intermittent claudication, ten with critical ischaemia; 14 men) underwent DSA and MRA-G. Gadolinium (40 ml, $0{\cdot}1\ \mathrm{mmol\ l^{-1}}$) was delivered via a peripheral vein over 2 min and scanning performed on a state of the art 1·5-T magnet. MRA images were acquired in 90 s over the abdomen/pelvis, thighs and legs (30 s each) providing images from the diaphragm to the foot. Reformatting allowed multiplanar views of all segments after a single contrast injection and scan.

Results All MRA-G studies were technically successful. Both the MRA-G and DSA films were assessed by two radiologists and two vascular surgeons. All occlusions or stenoses demonstrated by DSA were apparent on MRA-G. Furthermore, patent crural vessels were detected by MRA-G in four patients when not evident on DSA. In all patients the therapeutic decision based on MRA-G was identical to that for DSA.

Conclusion This study suggests that MRA-G may have a primary role for the rapid, non-invasive evaluation of patients with peripheral vascular disease. It provides images of comparable quality to DSA but with additional advantages of multiplanar views in all segments, routine demonstration of the whole of the intra-abdominal aorta and its branches, and enhanced imaging of crural vessels.

Identification of the unstable carotid plaque

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Background The aim of this study was to determine the relationship between ultrasonographically evaluated carotid plaque homogeneity (HOM) and the degree of carotid stenosis on duplex imaging with the incidence of ipsilateral cerebral infarction on computed tomography (CT) and cerebrovascular symptoms.

Methods A total of 150 consecutive patients with 192 plaques, 81 symptomatic and 111 asymptomatic, having 50–99 per cent carotid stenosis, were studied. Patients with cardioembolic symptoms were excluded. All ultrasonographic images of plaques were standardized in a computer so that the grey-scale median of blood was 0–5 and that of adventitia 180–200 on a linear scale from 0 to 255 (interobserver variability, $r=0{\cdot}93$). Homogeneity, a measure of the variability of tone in the neighbouring pixels, was evaluated with the spatial grey level dependence matrix method. The stenosis was evaluated on duplex imaging and the presence or absence of ipsilateral cerebrovascular symptomatology and CT infarction (discrete subcortical, large and small cortical which are probably thromboembolic) was noted.

Results A HOM of less than 0·3 and stenosis less than 70 per cent identified a group with an 11 per cent incidence of symptomatic plaques and a 16 per cent incidence of plaques associated with ipsilateral cerebral CT infarction. A HOM of less than 0·3 and stenosis equal to or greater than 70 per cent identified a group with incidences of 39 and 17 per cent respectively. A HOM equal to or greater than 0·3 and stenosis equal to or greater than 70 per cent identified a (high-risk) group with incidences of 59 and 37 per cent. A HOM equal to or greater than 0·3 and stenosis less than 70 per cent identified a group with incidences of 41 and 33 per cent respectively ($P<0{\cdot}05$, χ^2 test).

Conclusion These results indicate that computer-evaluated plaque homogeneity and degree of stenosis can identify plaques at high risk of cerebral CT infarction and symptoms, therefore having a potential application in the management and natural history studies of carotid plaques.

Influence of detection of silent cerebral infarction by magnetic resonance imaging on the management of carotid disease

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Background Whilst carotid endarterectomy (CEA) is usually performed for symptoms matched by a greater than 70 per cent stenosis of the relevant artery, silent cerebral infarction (SCI) may also occur in association with carotid atherosclerosis and such patients might benefit from surgery. Similarly SCI detected after CEA has been suggested as one endpoint by which potential benefits of different surgical or anaesthetic techniques can be assessed.

Methods Magnetic resonance imaging (MRI) scans performed 24 h before and after CEA in 46 patients were examined by a neuroradiologist blinded to the clinical details in order to determine the prevalence of SCI both after operation and in association with moderate (30–69 per cent) and severe (more than 70 per cent) asymptomatic stenoses in the contralateral hemisphere.

Results Preoperative MRI demonstrated infarcts in 38 of 92 (41 (95 per cent confidence interval (c.i.) 31–51) per cent) hemispheres, 20 of which were associated with a previous cerebrovascular accident, seven with an apparent transient ischaemic attack and 11 with SCI for which there were no symptoms or signs (assessed by neurologist). In the SCI group seven infarcts occurred in 22 hemispheres ipsilateral to 30–69 per cent stenoses (32 (95 per cent c.i. 12–52) per cent), three in 13 hemispheres (23 (95 per cent c.i. 0–46) per cent) ipsilateral to more than 70 per cent stenoses and one with a less than 30 per cent stenosis. Only two new cerebral infarcts were evident after CEA, one in a patient with a previous hemiparesis who had no new signs and one following the onset of symptoms 30 min before surgery.

Conclusion Thus, despite a previous report, SCI following CEA is uncommon and as a consequence postoperative MRI will not increase the power of trials to detect an advantage between different surgical or anaesthetic techniques. In contrast MRI evidence of SCI in patients with both moderate and severe asymptomatic stenoses is common and could identify additional patients who might benefit from CEA.

Value of varicose vein surgery

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Background The incidence of varicose vein surgery in the population is high. Recently there has been a call to reduce surgery for this condition as it is often seen as cosmetic. This study assessed whether surgery for varicose veins significantly affects the patient's health-related quality of life (HRQL).

Methods The SF36 health questionnaire and Aberdeen Varicose Vein Questionnaire (AVVQ) (a previously validated specific measure of health outcome) were administered to 98 consecutive patients undergoing surgery for primary varicose veins. Patients were followed up 6 weeks after surgery (response rate 77 per cent) and repeated the questionnaires. Of the respondents there were 51 women (68 per cent) and the mean age was 47 years. Analysis was performed for reliability and responsiveness and changes in HRQL.

Results The reliability estimates (Cronbach's alpha) for the eight scales of the SF36 were all above 0·7 (range 0·74–0·87), and were 0·74 for the AVVQ. The mean preoperative scores for the eight scales of the SF36 were not significantly different from age- and sex-adjusted UK norms. The mean scores following surgery for six of the eight scales of the SF36 improved but not significantly ($P > 0{\cdot}4$, paired sample t test). The AVVQ scores improved significantly ($t = 4{\cdot}653$, $P < 0{\cdot}0001$). Standardized response mean for the AVVQ was 0·54 indicating that the AVVQ is able to detect clinically important changes in HRQL.

Conclusion Surgery for varicose veins leads to a significant increase in HRQL and use of the above instruments may help justify the use of scarce national health service resources.

Effect of angle and Miller cuff on impedance at end-to-side anastomoses

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Background Impedance is a measure of resistance in pulsatile circuits and may be used to describe the consequent flow disturbance associated with end-to-side anastomoses (ESAs). Changes in the geometry of ESAs are known to alter flow, distribution of shear forces and the dissipation of energy. The addition of a vein cuff is said to establish vortices that change the distribution of shear stress and favour an increase in patency. Since impedance is affected by ESA geometry, impedance analysis may be able to identify a haemodynamically ideal ESA. The effect of ESA geometries on impedance was investigated.

Methods ESAs were constructed from fixed lengths of polytetrafluoroethylene (inflow vessel 6 mm in diameter, outflow vessel 4 mm in diameter) in a standardized manner at various angles (15–120°) with and without a cuff (c). The ESAs were connected to a pulsatile pump delivering physiological flows (50–400 ml min^{-1}) and pressures (mean 50–100 mmHg). The pulse volume (P) and flow (Q) proximal to the ESA were measured with a pressure cuff and Doppler probe respectively, on a PVL-50 (SciMed, UK). The ratio P/Q was measured as a function of frequency to give an impedance index.

Results The values in the *Table* show impedance index (median of nine readings) at various flow rates. Repeatability was 0·05.

Flow (ml min^{-1})	15°	15°c	30°	30°c	45°	45°c	60°	60°c	90°	120°	120°c
100	0·85	0·71	1·02	0·95	1·20	1·09	1·36	1·21	1·49	1·75	1·71
200	1·10	0·93	1·32	1·25	1·49	1·38	1·63	1·50	1·79	2·15	1·95
300	1·17	0·95	1·43	1·33	1·55	1·50	1·72	1·61	1·80	2·24	1·96
400	1·20	1·02	1·42	1·34	1·57	1·51	1·72	1·62	1·81	2·18	1·99

$P < 0{\cdot}05$ at each flow rate (analysis of variance)

Conclusion At physiological flow rates, decreasing the angle of an ESA and/or constructing a Miller cuff reduces the impedance index of the anastomosis. This may explain the better patency rates observed in femoropopliteal grafts with a vein cuff.

Homocysteine induces endothelial cell dysfunction

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Background Despite recognition of homocysteine as an independent risk factor for atherogenesis, the mechanism of its atherogenicity remains unclear. This study assessed the effect of homocysteine on endothelial cell (EC) proliferation as a measure of its reparative capacity. EC function was also assessed by measuring nitric oxide and endothelin (ET-1), as both are indicators of atherogenicity.

Methods Human umbilical vein endothelial cells at passage 2–3 were treated with D,L-homocysteine (Sigma) at concentrations of 0, 0·01, 0·02, 0·05, 0·1, 1·0, 2·5 and 5 mmol l^{-1} for 24 h. EC proliferation was assessed using a 5-bromo-2′-deoxyuridine labelling and detection kit (Sigma). Nitric oxide production was measured using the Griess reaction after 24 and 48 h. ET-1 production was measured in the supernatant at 12, 24 and 48 h using a human ET-1 enzyme-linked immunosorbent assay kit (R and D).

Results

Homocysteine (mmol l^{-1})	Percentage decrease in proliferation	Nitric oxide production (μmol l^{-1}) 24 h	Nitric oxide production (μmol l^{-1}) 48 h	ET-1 production (mmol l^{-1}) 24 h	ET-1 production (mmol l^{-1}) 48 h
0	0	0·77	2·50	63	67
0·01	30	0·36	0·65	66	108
0·10	43	0·36	0·66	74	111
1·00	49	0·38	0·78	53	89
2·50	52	0·40	0·79	30	47
5·00	54	0·42	0·79	26	37
P*	< 0·02	< 0·03	< 0·05	< 0·02	< 0·02

*Analysis of variance

Conclusion Homocysteine inhibited EC proliferation, reduced nitric oxide concentration and upregulated ET-1 production. The increase in ET-1 concentration declined at around homocysteine 1 mmol l^{-1} suggesting EC toxicity. These data suggest an endothelium-dependent mechanism for the atherogenic effects of homocysteine.

Sympathetic skin response and patient satisfaction on long-term follow-up of thoracoscopic sympathectomy for hyperhidrosis

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Background Sympathetic skin response (SSR) is a measure of evoked endosomatic electrodermal activity. Patients with hyperhidrosis have abnormal SSRs which are abolished immediately following thoracoscopic sympathectomy. Absence of SSRs has been proposed as an objective measure of successful outcome following sympathectomy. A study was carried out to determine the effect of sympathectomy on SSR during long-term follow-up.
Methods Patients who had undergone bilateral thoracoscopic sympathectomy for hyperhidrosis underwent postoperative assessment of SSRs. A 15-mA stimulus was applied over the median nerve contralateral to the sympathectomy and evoked electrodermal activity was recorded from the sympathectomized palm. SSRs were analysed for amplitude. Patient satisfaction with surgery was assessed on a visual analogue scale (0–1·0).
Results Twenty-six patients were examined; 21 were female. Mean (range) age was 23 (9–36) years. Mean (range) follow-up was 39 (4–138) months. Twenty-four patients graded preoperative symptoms as severe. In three patients residual or recurrent symptoms occurred. Mean (range) patient satisfaction was 0·79 (0·06–1·0). In only seven of 52 palms were recurrent SSRs not detected.

SSRs	Amplitude (μV)
Mean (range)	714 (0–2906)
Normal	800–2000

Repeated-measures analysis of variance found no correlation between amplitude of SSR and time since surgery ($F = 0·48$, $P = 0·49$) or patient satisfaction.
Conclusion Following sympathectomy SSRs are not permanently abolished, but return of SSRs does not correspond with symptom recurrence or patient satisfaction. As such, SSRs are a poor tool for objective assessment of long-term outcome following sympathectomy.

Flow fields in *in vitro* end-to-side anastomoses: effect of disease progression and angle

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Background The addition of a distal vein cuff to a femorotibial polytetrafluoroethylene graft may improve patency but does not prevent the formation of intimal hyperplasia (IH). A flow vortex exists at the 'heel' of the cuff where shear stress is low and bloodborne factors which take part in thrombus formation or promote IH have an increased residence time. Little is known about the behaviour of this vortex with changing flow rate caused by disease progression.
Methods A flow circuit comprising a pulsatile pump was connected to polished glass models of standard or cuffed (height 1 or 2 cm end-to-side anastomoses (ESAs)) (inflow diameter 6 mm; outflow diameters 2 mm, angles 15, 30, 45, 60°). The proximal outflow channel was occluded 2 cm from the heel. The motion of illuminated particles was captured on video and analysed frame by frame to measure the maximum vortex height. Flow rate was altered by a clamp on the inflow or outflow tubing simulating progression of disease.
Results Values in the *Table* are vortex height in pixels (median of five measurements).

Flow (ml min^{-1})	Standard ESA 80	Standard ESA 100	Standard ESA 120	1-cm cuff 80	1-cm cuff 100	1-cm cuff 120	2-cm cuff 80	2-cm cuff 100	2-cm cuff 120
15°	44	41	42	77	77	79	121	119	122
30°	53	53	52	81	80	80	130	132	131
45°	68	66	69	95	96	96	150	148	151
60°	81	79	83	113	113	113	175	172	174

Conclusion Vortex height does not change with flow rate for a given cuff angle and ESA type, but increases with anastomotic angle ($P < 0·05$, analysis of variance) and cuff height. The development of IH may be favoured by a tall cuff (large vortex) whereas a long and low cuff (shallow angle ESA, small vortex) may be able better to accommodate any IH before it causes a significant flow reduction. Although the small vortex is in a shallow standard ESA, the ESA volume may not be large enough to compensate for any IH that develops.

Treatment of internal carotid artery thrombosis: an *in vitro* model

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Background This study compared the ability of commercially available thrombectomy catheters to clear thrombus from an *in vitro* model of complete internal carotid artery (ICA) thrombosis.
Methods A glass model of the ICA was filled with human blood which was allowed to coagulate. The Hydrolyser (Cordis, The Netherlands), Clot Buster (Microveena, USA), Acolysis System (Angiosonics, USA), Angiojet (Possis Medical, USA) and an Intimax Embolectomy Catheter (Applied Medical, USA) were each tested for pressure changes distal to catheter tip on activation and ability to clear the thrombus from the model.

Results

Catheter	n	Pressure change (mmHg)	Model clearance (%)*
Clot Buster	8	− 50	89·0 (71·5–95·8)
Hydrolyser	9	− 30	79·9 (53·2–93·0)
Balloon	5	< − 50 to > + 50	90·0 (86·9–94·8)
Acolysis	7	0	33·8 (11·8–49·8)
Angiojet	8	− 30 to + 100	94·7 (92·2–97·5)

*Values are median (range)

The Clot Buster produced the lowest tip pressure. Both the balloon catheter and the Angiojet created positive pressures distal to the tip with the potential for distal embolization. The clearance achieved by the Clot Buster and the Hydrolyser were not significantly different to that produced by the balloon catheter and the Angiojet (Kruskall–Wallis test). Furthermore, the Clot Buster and Hydrolyser are easier and cheaper to use.
Conclusion So far, the Clot Buster and the Hydrolyser show the greatest potential for use in carotid endarterectomy with complete ICA thrombosis.

Hypocoagulability and failure of compression ultrasonography for false aneurysm

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Background False femoral artery aneurysm is an occasional complication of percutaneous cardiovascular radiological procedures. Compression ultrasonography causes thrombosis non-invasively, reducing need for operative intervention. The technique fails in a proportion of cases. Analysis was undertaken to identify causes of failure.
Methods Patients presenting with false femoral artery aneurysm since 1984 were identified from a computerized database (BIPAS). Since 1993 compression ultrasonography has been performed as first-line treatment according to a standard protocol. The aneurysm jet is located and compressed with the 5-MHz probe of an ATL Ultramark 9 colour flow duplex scanner. Up to three 10-min compressions are performed per treatment. Prospectively collected ultrasonographic data and case notes were reviewed to identify causes of failed compression.
Results False femoral artery aneurysm occurred as a complication in 27 (0·1 per cent) of 24 033 cardiovascular radiological procedures. Fifteen aneurysms were treated by compression. The technique was successful in nine of 15 cases but primary failure occurred in six. Five of six had abnormal clotting ($\chi^2 = 7{\cdot}17$, $P = 0{\cdot}005$); three were anticoagulated and compression was subsequently successful in two of these patients following reversal of warfarin therapy. In three of 15 cases surgical repair was necessary. Size of aneurysm, velocity of flow jet and size of endoluminal catheter were not found to be significant factors in failure of treatment.
Conclusion Compression ultrasonography is an effective treatment of false femoral aneurysm. Hypocoagulability reduced effectiveness. For patients in whom anticoagulation cannot be reversed, primary surgical repair should be considered.

Tetracycline modulates cytokine secretion in human abdominal aortic aneurysms

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Background Paracrine interactions between inflammatory and collagen synthesizing cells appear to be important in the growth of abdominal aortic aneurysms. Interrupting these processes with drugs provides a potential method of limiting aneurysm expansion.
Methods Explant cultures of human aorta have been established and characterized to investigate collagen metabolism and cytokine production in the aneurysm wall. How collagen turnover (hydroxyproline secretion) and cytokine release (measured by enzyme-linked immunosorbent assay) are influenced by tetracycline is now reported.
Results Histological examination demonstrated preservation of explant tissue architecture for up to 6 days. The concentration of hydroxyproline released into the culture medium was unchanged in the presence of tetracycline at either 10 or $100\,\mu g\,ml^{-1}$. The explants secreted the cytokine monocyte chemotactic protein 1 (MCP-1) but not tumour necrosis factor α or interferon γ. The release of MCP-1 was reduced in the presence of tetracycline in a concentration-dependent manner.

Conditioned medium at 48 h	Control	Tetracycline ($\mu g\,ml^{-1}$)	
		10	100
Hydroxyproline ($\mu g\,ml^{-1}$) ($n = 9$)	31·4(7)	32·4(9)	29·4(5)
MCP-1 ($ng\,ml^{-1}$) ($n = 5$)	18·9(11·8)	16·5(6)	5·2(2·8)*

Values are mean(s.d.). *$P < 0{\cdot}01$

Conclusion Macrophages are the source of collagen-degrading enzymes in the aneurysm wall. The ability of tetracycline to inhibit secretion of MCP-1, the most potent attractant for macrophages, might translate clinically to reduced aneurysm expansion.

Antioxidant capacity in vascular patients in relation to nutrition or severity of ischaemia

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Background Previous work indicates that a reduced total antioxidant capacity (TAC) increases the risk of postoperative infection in patients undergoing femorodistal bypass. However, it is not known whether such a reduction is dependent upon the severity of ischaemia or the patient's nutritional status.
Methods The TAC and nutritional status of two groups of patients with differing severities of vascular disease (14 (nine men, median age 72 years) with critical limb ischaemia (rest pain, ankle pressure less than 50 mmHg); 13 claudicants (seven men, median age 68 years)) has been compared with that of ten controls (six men, median age 64 years). Nutritional status was assessed by mid-arm circumference, triceps skinfold thickness, body mass index, lean body mass, maximum voluntary contraction (hand grip dynamometer), bioelectrical impedance, and levels of serum albumin, prealbumin and transferrin. These markers were then correlated with TAC.
Results Patients with peripheral vascular disease had a lower median TAC than controls (752 *versus* $1130\,\mu mol\,l^{-1}$; $P < 0{\cdot}05$, Mann–Whitney U test) although there was no difference between claudicants and patients with critical ischaemia (789 *versus* $721\,\mu mol\,l^{-1}$). However, TAC did correlate with maximum voluntary contraction ($r_S = 0{\cdot}64$, $P = 0{\cdot}037$), lean body mass ($r_S = 0{\cdot}60$, $P = 0{\cdot}043$) and serum transferrin level ($r_S = 0{\cdot}67$, $P = 0{\cdot}02$).
Conclusion These results indicate that TAC is influenced by nutritional status rather than the severity of ischaemia. Thus the risk of postoperative sepsis might be reduced by preoperative augmentation of both antioxidant and nutritional status before either limb salvage surgery or operation for claudication.

Hyperhomocysteinaemia, peripheral vascular disease and neointimal hyperplasia in elderly patients

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Background Hyperhomocysteinaemia is a reported risk factor in patients with premature peripheral vascular disease (PVD) and in vein bypass grafts with neointimal hyperplasia (NIH). Its prevalence in a more typical group of vascular patients is unknown. The aims of this case-controlled study were to determine the prevalence of hyperhomocysteinaemia in unselected patients with PVD and in patients with NIH.
Methods Homocysteine was measured in fasting plasma from subjects and controls in a high-pressure liquid chromatography assay. Control results were logarithmically transformed for a reference range (mean plus two standard deviations) of 8·86–14·25 μmol l^{-1}.

	Controls ($n=30$)	PVD ($n=35$)	NIH ($n=15$)
Homocysteine (μmol l^{-1})	11·30 (9·37–14·07)	15·80 (11·10–19·50)*	12·00 (6·90–14·20)†

Values are median (interquartile range). *$P=0{\cdot}001$, †$P=0{\cdot}72$ *versus* controls (Mann–Whitney U test)

Results Hyperhomocysteinaemia (homocysteine greater than 14·25 μmol l^{-1}) was present in seven of 30 controls and 22 of 35 patients with PVD ($\chi^2=10{\cdot}212$, $P=0{\cdot}001$ *versus* controls) but in only three of five patients with NIH ($\chi^2=0{\cdot}064$, $P=0{\cdot}80$ *versus* controls). Serum folate concentrations in the patients with PVD were lower than those in patients with NIH: mean(s.e.m.) 4·5(0·3) *versus* 7·6(1·1) μmol l^{-1} respectively ($P=0{\cdot}015$, t test).
Conclusion Hyperhomocysteinaemia is strongly associated with PVD and this association appears even stronger than in patients with premature PVD. In contrast to a previous report there was no association with NIH and this may be attributable to differences in folate concentrations.

Cytokine response to perioperative leucodepletion during limb salvage surgery

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Background Polymorphonuclear neutrophils (PMNs) promote ischaemia–reperfusion (IRI), and PMN depletion by both mechanical and immunological methods has been shown to ameliorate this injury in animal models. However, thus far leucodepletion has not been subjected to clinical assessment.
Methods In ten patients undergoing limb salvage surgery the effect of PMN depletion (using a double-lumen femoral venous catheter, extracorporeal circuit, leucocyte filter, and flow rates of 200 ml min^{-1} for 15 min (3000 ml or approximately 60 per cent of blood volume filtered) on levels of interleukin (IL) 6, IL-8 and tumour necrosis factor (TNF) α were compared with the same measurements in ten control patients undergoing similar surgery. Samples were taken from both peripheral (PER) and femoral (FEM) venous blood at baseline, reperfusion (T_0), 4 h, 24 h, 3 and 6 days (T_4, T_{24}, T_{3D} and T_{6D}).
Results Except at baseline, levels of IL-6 were lower in the patients who had filtration at all time points. These differences (filtered *versus* control, expressed as median percentage change from baseline) were significant at T_0 FEM (+122 *versus* +148 per cent, $P<0{\cdot}0001$), T_0 PER (+15 *versus* +52 per cent, $P<0{\cdot}0001$), T_{3D} (+79 *versus* +444 per cent, $P=0{\cdot}025$) and T_{6D} (−24 *versus* +221 per cent, $P=0{\cdot}046$). TNF-α levels were higher in those who had leucodepletion, particularly at T_0 PER (−16 *versus* −17 per cent, $P<0{\cdot}0001$) and T_4 PER (−9 *versus* −43 per cent, $P<0{\cdot}0001$). Levels of IL-8 were lower in the PER samples (T_0 +1·8 *versus* +4·1 per cent, $P<0{\cdot}0001$; T_{24} +2 *versus* +125 per cent, $P<0{\cdot}0001$) but higher in FEM samples (T_4 +24 *versus* +5 per cent, $P<0{\cdot}0001$; T_{24} +72 *versus* +49 per cent, $P<0{\cdot}0001$) of patients who had filtration.
Conclusion This novel study of intraoperative PMN depletion is associated with changes in the cytokine profile that would be consistent with amelioration of IRI. Thus levels of the PMN-dependent proinflammatory cytokine IL-6 were reduced, whilst those of IL-8 in femoral blood increased (leucocyte adhesion inhibition effect). Similarly peripheral TNF-α levels were higher and this should suppress PMN release from bone marrow reserves. The incidence of infective complications, amputations and death was comparable in the two groups. This technique appears safe, and its therapeutic role warrants further investigation.

Upregulation of mesothelial heparin-binding epidermal growth factor by peritoneal cytokines: implications for tumour metastases

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Background Heparin-binding epidermal growth factor (HB-EGF) is a newly characterized growth factor which is mitogenic for EGF receptor-positive tumour cells and shares similar heparin-binding properties to basic fibroblast growth factor (bFGF). It is upregulated in endothelial cells by the cytokines tumour necrosis factor (TNF) α and interleukin (IL) 1β which are abundant in the peritoneal cavity after operation. The aim of the present study was to determine their effect on human mesothelial expression of HB-EGF and bFGF.
Methods Samples of human omentum (ethics committee approved) were enzymatically digested and used to establish mesothelial cell cultures. Confluent cells were stimulated with commercial TNF-α and IL-1β or postoperative drain exudate and subjected to semiquantitative reverse transcription–polymerase chain reaction using gene-specific primers for HB-EGF, bFGF and the house-keeper gene glyceraldehyde-3-phosphate dehydrogenase.
Results Mesothelial cells showed a low constitutive expression of HB-EGF and bFGF messenger RNA. TNF-α and IL-1β significantly stimulated HB-EGF expression in a dose- and time-dependent manner, maximally at 1 ng ml^{-1} and 4 h; bFGF expression was unchanged. In the *Table*, results for a 4-h incubation are expressed as a ratio of growth factor : glyceraldehyde-3-phosphate dehydrogenase amplified products normalized for controls (no stimulation).

	HB-EGF	bFGF
TNF-α (1 ng ml^{-1}) ($n=6$)	3·2 (2·9–3·9)*	1·1 (0·9–1·2)
IL-1β (1 ng ml^{-1}) ($n=6$)	2·7 (1·5–3·2)*	1·0 (0·7–1·2)

Values are median (interquartile range). *$P=0{\cdot}03$ (Wilcoxon signed rank test)

A similar increase in HB-EGF expression occurred following incubation with drain exudate, and was attenuated by pretreatment with anti-IL-1 and anti-TNF antibodies.
Conclusion The cytokine environment of the postoperative peritoneal cavity results in the production by human mesothelial cells of a growth factor (HB-EGF), which is known to be mitogenic for gastrointestinal cancer. These findings have profound implications for the aetiology and prevention of local tumour recurrence.

Drug resistance evaluation by functional assay and immunofluorescence in bladder cancer

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Background Superficial bladder cancer frequently recurs and can evoke repeated chemotherapy. However, multidrug resistance (MDR) limits the effectiveness of chemotherapy.
Methods MDR was assessed in recurrent bladder cancer ($n = 11$) by: (1) immunofluorescent staining of three proteins associated with MDR, P-glycoprotein (P170), MDR-related protein (MRP) and lung resistance protein (LRP) in frozen sections; and (2) confocal microscopy of epirubicin accumulation ($20\,\mathrm{mg\,ml^{-1}}$, 2 h) in primary explants in culture. Specifically, intracellular drug distribution was determined including changes under the influence of the MDR reversing agents, verapamil and PSC833. Five cell lines (including resistant variants) were used for method development and afforded the 'gold standard' results for both assays.
Results Seven of 11 specimens exhibited positive immunofluorescence: five for P170 with or without other MDR proteins, one for MRP and one for LRP, with the percentage of stained cells usually below 15 per cent. Of the seven immunohistochemically resistant cancers, only five showed a resistant pattern of epirubicin uptake in culture, i.e. less total drug uptake compared with sensitive cultures (three to ten times), nuclear exclusion of drug, reversal of the latter pattern using verapamil and/or PSC833. Of the four specimens with negative immunofluorescence, two grew explants that were resistant *in vitro*. Overall, only seven of 11 specimens gave matching results using both assays (sensitive/sensitive or resistant/resistant).
Conclusion These early results show that both immunofluorescence and functional assays give information on MDR status. The majority of tumours showed at least small populations of resistant cells. The clinical implication is that reversal strategy should be developed for early or prophylactic implementation.

Colorectal tumours are highly heterogeneous in chromosome number at the single cell level

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Background The multistep hypothesis for colorectal carcinogenesis proposed by Vogelstein involves genes located on a number of chromosomes. In particular, chromosomes 7, 17 and 18 have been reported to carry critical genes. In this study a three-colour fluorescence *in situ* hybridization (FISH) approach was used to investigate the number of these three chromosomes within individual tumour cells to determine tumour heterogeneity. The FISH data were also correlated with the gross ploidy index of the tumour.
Methods Tumour biopsies ($n = 50$) were taken from a non-necrotic region of tumour and touch-preparations were made on to Vectabond-treated microscope slides. These slides were used in FISH experiments with three pericentromeric chromosome probes: chromosome 7 was detected with fluorescein isothiocyanate (FITC), chromosome 17 with Texas Red, and chromosome 18 with a mixture of FITC- and Texas Red-labelled probes. One slide was Feulgen stained for quantitative image analysis using a CAS image analyser.
Results FISH analysis showed a high level of heterogeneity in the vast majority of samples. The most frequently occurring modal chromosome profile was 2/2/2 (41 per cent) for chromosomes 7, 17 and 18 respectively, although the ploidy index of these tumours varied from 0·93 to 2·06 with no correlation to histological stage. A modal profile of (3/4)/2/2 was the most commonly found profile in Dukes B (eight of 19) and C (six of 16) tumours but again no correlation with DNA ploidy was observed.
Conclusion This study shows that tumours are highly heterogeneous at the single cell level and that a modal chromosome profile does not correlate directly with total DNA ploidy or histology of a tumour. It is hypothesized that tumour outcome may be better predicted by the presence of particular subpopulations of cells found within a tumour mass rather than by total DNA ploidy.

Suicide gene therapy for colorectal liver metastases: evidence of a systemic antitumour immune response

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Background Expression of the herpes simplex virus type 1 thymidine kinase (HSV1-TK) gene in localized tumours results in tumour regression following the administration of ganciclovir (GCV). A localized immune response contributes to this regression. The aim of this study was to determine if the treatment of localized HSV1-TK-expressing colorectal liver metastases resulted in a systemic antitumour immune response and the regression of distant metastases. The effect of HSV1-TK expression in the absence of drug selection was also investigated.
Methods Liver metastases were generated by the subcapsular injection of 5×10^6 cells of the K12TK cell line (groups 1 and 2) and K12 cell line (group 3) in BDIX rats. All animals received a second injection of the K12 cell line in an adjacent lobe of the liver. After 7 days, group 2 was treated with intraperitoneal GCV $75\,\mathrm{mg\,kg^{-1}}$ twice daily for 5 days. Animals were killed, tumour volumes were determined and T cell cytotoxicity assays performed. Experiments were performed under the Animals (Scientific Procedures) Act 1986.
Results HSV1-TK-expressing tumours showed marked regression following GCV (group 2): mean tumour volume $0{\cdot}6\,\mathrm{mm}^3$ compared with $98{\cdot}4\,\mathrm{mm}^3$ for controls (group 3) ($P < 0{\cdot}0001$, Mann–Whitney U test). However, HSV1-TK protein expression alone also resulted in tumour regression (group 1): mean tumour volume $22{\cdot}4\,\mathrm{mm}^3$ ($P < 0{\cdot}05$). Adjacent tumours in group 2 had a mean tumour volume of $45{\cdot}2\,\mathrm{mm}^3$ (P not significant), whilst those in group 1 showed significant regression: mean tumour volume $20{\cdot}2\,\mathrm{mm}^3$ ($P < 0{\cdot}05$). A cytotoxic T cell population recognizing the unmodified K12 cell line was identified in group 2.
Conclusion HSV1-TK-mediated therapy of experimental liver metastases results in a systemic antitumour immune response. The TK protein appears to have a role in the generation of antitumour immunity.

Frequent G to T transversion at codon 249 of the *p53* tumour suppressor gene in hepatocellular carcinoma

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Background Hepatocellular carcinoma (HCC), a common malignancy in south-east Asia, accounts for over 1 000 000 deaths per year worldwide. In Hong Kong, HCC is the second leading cause of cancer death. Both exposure to dietary carcinogens such as aflatoxin B_1 and infection of hepatitis B virus have been implicated as important risk factors for the development of HCC. The genetic mutation of the *p53* gene in HCC was studied.
Methods DNA extracted from 52 operative tumour samples of HCC was used. Point mutations were detected by single-stranded conformational polymorphism and direct DNA sequencing techniques.
Results Within exons 5–8 of the *p53* gene, 17 point mutations were detected in the 52 samples. The frequencies of point muta-

tion in exons 5, 6, 7 and 8 were four of 17, three of 17, nine of 17 and one of 17 respectively. Furthermore, eight of the nine point mutations in exon 7 were found to be G to T transversion at codon 249.
Conclusion These findings suggest that G to T transversion at codon 249 of the *p53* tumour suppressor gene was a common genetic alteration in this series. As such transversion is commonly found in HCC because of dietary exposure to aflatoxin B_1, this may represent a subset of HCC in Hong Kong.

Desmoid precursor lesions

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Background Germline mutations of the *APC* tumour suppressor gene on chromosome 5q22 are responsible for familial adenomatous polyposis (FAP). Desmoid tumours are poorly understood, locally invasive, non-metastasizing neoplasms that occur in about 10 per cent of patients with FAP. The natural history of desmoids was investigated by documenting prospectively the prevalence and progression of possible precursor lesions, and comparing the somatic genetics of these with established desmoid tumours.
Methods A group of patients with FAP and controls were examined at laparotomy. Another group, with FAP and no clinical evidence of desmoid, and a group of controls underwent helical abdominopelvic computed tomography. DNA from 17 desmoids (from 13 patients with FAP) and from eight putative precursor lesions biopsied at laparotomy was assessed for allele loss at five dinucleotide repeat microsatellite markers flanking *APC*. Mutations in *APC* exon 15 were detected using heteroduplex analysis of overlapping polymerase chain reaction products and the protein truncation test. Regions found to contain mutations were directly sequenced.
Results At laparotomy, 13 of 42 patients with FAP had fibromatous mesenteric plaques; seven had no history of surgery. Seven had more extensive mesenteric fibromatosis; these individuals had undergone significantly more laparotomies than the rest. Of 103 patients scanned, two had desmoid tumours and 22 (21 per cent) had mesenteric fibromatosis. On follow-up both desmoid tumours grew rapidly; mesenteric fibromatosis was unchanged in five and resolved in four of the nine patients rescanned. Somatic mutation was identified in 11 of 17 desmoids and allele loss at *APC* in two. No somatic abnormalities of *APC* were detected in the putative precursors ($P<0\cdot05$, Fisher's exact test), all of which were histologically compatible with desmoid.
Conclusion A model of desmoid tumour development, analogous to the adenoma–carcinoma sequence, is proposed, in which a less benign phenotype emerges as molecular genetic abnormalities accumulate. Mesenteric plaque-like desmoid precursor lesions arise before surgery in many patients with FAP as a result of abnormal fibroblast function; some, perhaps stimulated by surgery, progress to mesenteric fibromatosis; these in turn can give rise to a desmoid tumour.

Nucleotide excision–repair of damaged DNA is inhibited by doxorubicin in human tumour cells

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Background Nucleotide excision–repair (NER) removes DNA damage induced by ultraviolet (UV) radiation or by cisplatin and may affect tumour chemosensitivity. This study assayed NER in human adenocarcinoma cells and assessed effects of doxorubicin on this process.
Methods NER was assessed by tumour cell reactivation of UV-damaged DNA of the chloramphenicol acetyltransferase (CAT) reporter gene. DNA damage impairs CAT activity. Any subsequent increase of activity indicates NER and provides a quantitative assay. UV-damaged and normal CAT genes were incorporated into recombinant adenoviral vectors (UV Ad-CAT and Ad-CAT respectively) which were used to infect cells. CAT activity was assessed by radioligand binding assay. Effects of doxorubicin were then assayed.
Results High levels of CAT activity were induced by infection with undamaged Ad-CAT (mean(s.d.) 30(3) to 45(8) *versus* 5(2) c.p.m. in control). CAT activity levels were initially low (8(2) c.p.m. on day 1) after infection by UV Ad-CAT, but subsequently increased to 18(2) c.p.m. by day 4, indicating effective NER. Doxorubicin inhibited NER in cells infected with UV AD-CAT, and CAT activity remained low (8(2) c.p.m. on day 4).
Conclusion Human adenocarcinoma cells have high NER activity which could impair responsiveness to cisplatin. Doxorubicin inhibits NER and may enhance chemosensitivity.

Correlation of a colour subtraction pulse sequence for magnetic resonance-guided interstitial thermoablation with temperature and histological lesion size

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Background Magnetic resonance (MR) imaging is the most sensitive modality for monitoring interstitial laser thermotherapy (ILT). However, dependence on interpretation of grey-scale changes and variable tissue T1 times make it less than ideal. A prototype real-time pulse sequence (General Electric (GE), USA) that assigns a colour spectrum to grey-scale changes will potentially increase the accuracy of MR-guided thermal surgery. However, the spectrum must be calibrated with temperature and image-predicted necrosis correlated with histological effect to allow its clinical use.
Methods Porcine livers were placed within a 0·5-T GE SP10 Interventional MR Unit. A 600-μm neodymium yttrium–aluminium–garnet laser fibre (wavelength 1064 nm) with diffuser tip was placed in the liver parenchyma with an MR-compatible thermocouple. A sagittal MR image containing the fibre tip was chosen as the template. A 3-cm region of interest (ROI) was drawn centred on the fibre. Thermal lesions were produced (5 W, duration 20 min) with real-time colour subtraction MR monitoring throughout (FGR60, acquisition time 4 s). At 1-min intervals the pixel intensity value, temperature and colour at the laser tip were measured. Twenty burns were produced. The pixel intensity measurements were expressed as a percentage of the mean pixel intensity of the ROI to standardize measurements. Using the colour representing the temperature at which tissue necrosis would be expected to occur, predicted maximum lesion size was measured from the images and compared with histological assessment.
Results There was a linear relationship between temperature and percentage pixel change ($r=0\cdot84$). Six discrete colours were determined in the spectrum and all were significantly different from each other in terms of mean percentage pixel change ($P<0\cdot01$) and mean temperature ($P<0\cdot01$; except between orange and yellow, $P=0\cdot037$). Green had a mean(s.d.) temperature of 55·6(5)°C, and thus predicted necrosis. Image-predicted maximum lesion size correlated closely with histology ($r=0\cdot93$).
Conclusion The colour changes produced by this unique pulse sequence have been calibrated with tissue temperature *in vitro*. The colour representing a temperature above which necrosis is known to occur can be used accurately to predict lesion size. This will potentially allow greater accuracy and safety for MR monitoring of ILT *in vivo*.

Genomic heterogeneity in synchronous hepatocellular cancers

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Background Hepatocellular carcinoma (HCC) arising in a cirrhotic liver is frequently multifocal. Whether the smaller lesions represent intrahepatic metastases or *de novo* cancers has not been established. Their degree of genomic heterogeneity was assessed using arbitrarily primed polymerase chain reaction, a new but well validated technique of DNA fingerprinting not requiring prior sequence information.
Methods Sixty nodules (37 HCC, 23 regenerative nodules) were sampled from ten human cirrhotic livers removed at orthotopic liver transplantation. Tumour tissue was microdissected from paraffin-embedded formalin-fixed samples, and phenol extraction of genomic DNA was performed. Two arbitrary primers (AR3 and ZF3) were used to amplify the genomic DNA of each sample. Fingerprinting of the random amplified fragments was performed by acrylamide gel electrophoresis.
Results Marked genomic heterogeneity was noted amongst the nodules studied. No two cancers or regenerative nodules had identical electrophoretic patterns. Even HCCs in close proximity and within the same segment of the liver were found to have distinct genomic patterns.
Conclusion Such genomic heterogeneity in synchronous HCCs may explain the poor response to treatment of these cancers. Also, if the smaller tumours are *de novo* lesions rather than metastases, as these data suggest, then current concepts regarding liver resection as a curative treatment modality for HCC may require reassessment.

Protective role of the current preservation solutions against warm ischaemia in rat kidney

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Background The protective role of current preservation solutions in the prevention of warm ischaemic and reperfusion injury in a rat kidney model is reported. The solutions studied included Euro-Collins (EC), hyperosmolar citrate (HOC), phosphate-buffered sucrose (PBS140) and University of Wisconsin solution (UW).
Methods Male Wistar rats (300–350 g) were anaesthetized by intraperitoneal injection of inactin 120 mg kg^{-1}. An intravenous infusion was set up at 6 ml h^{-1} (sodium chloride 125 mmol l^{-1}, bicarbonate 25 mmol l^{-1}) also containing 37 MBq l^{-1} [^{3}H]inulin (for inulin clearance). Both ureters were cannulated for serial urine collection. An equilibration period of 1 h was allowed following surgery after which urine was collected for 1 h (control). The left kidney was then flushed with 0·5 ml 0·9 per cent saline, EC, HOC, PBS140 or UW at 37°C. A clamp was then applied to the left renal pedicle. After 45 min the clamp was released and a right nephrectomy was performed. Urine flow and composition from the left kidney were observed for 4 h. Home Office guidelines were strictly followed in all animal experiments.
Results Results are presented for inulin clearance, urine flow and urine osmolality in the third hour after ischaemia compared with preischaemic control values.

Function	Period	Saline	EC	HOC	PBS140	UW
GFR (μl min^{-1})	Before ischaemia	611(64)	839(146)	604(92)	721(96)	1125(128)
	After ischaemia	31(14)	146(108)	168(102)	365(87)	534(162)
Urine flow (μl h^{-1})	Before ischaemia	428(37)	530(154)	575(224)	468(76)	413(76)
	After ischaemia	607(282)	848(456)	1280(576)	1566(565)	1873(521)
Osmolality (mosm l^{-1})	Before ischaemia	1087(53)	1016(167)	1050(236)	1024(98)	1094(127)
	After ischaemia	331(8)	366(28)	436(28)	499(37)	519(45)

Values are mean(s.e.m.) ($n = 6$). GFR, glomerular filtration rate

Conclusion Forty-five minutes of warm ischaemia to rat kidney was considered very severe. Both PBS140 and UW provided effective protection resulting in high output of concentrated urine compared with EC and HOC.

Matrix metalloproteinases and angiogenesis in breast cell line co-cultures with fibroblasts

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Background Matrix metalloproteinases (MMPs) are crucial for the invasion and metastasis of breast tumour cell lines. The initial steps of angiogenesis also require basement membrane degradation and matrix protein remodelling. Production of these MMPs by fibroblasts is induced by breast carcinoma cell lines. Pollette *et al.* found that the invasive breast cell line MDA231 induced breast fibroblasts to produce MMP-1 and activate pro-MMP-2, but the less invasive cell line MCF-7 did not. Assessment of the angiogenic activity of these two cell lines in co-culture with fibroblasts, using the chick chorioallantoic membrane (CAM) model system, is presented.
Methods Using stereoscopic microscopy blood vessels invading a 20-μl collagen gel on the CAM were counted through a 2 × 2 mm nylon mesh over 5 days. MDA231 and MCF-7 cells were co-cultured on these gels with the slow-growing fibroblast cell line KB16F. Results are expressed as a percentage of mesh squares containing blood vessels.
Results MDA231 cells were more angiogenic when co-cultured with a fibroblast cell line that was not significantly angiogenic by itself. MCF-7 cells showed no such angiogenic advantage with fibroblasts.

Assay	*n*	Angiogenesis (%)	*P**
KB16F *versus* negative control	72	20 *versus* 18	0·135
MDA co-culture *versus* MDA alone	33	100 *versus*85	0·028
MCF-7 co-culture *versus* MCF-7 alone	54	85 *versus* 75	0·676

Values are median. *Mann–Whitney *U* test

Conclusion This breast fibroblast cell line is slow growing and displays contact inhibition *in vitro*. When incubated in isolation on the chick CAM it does not demonstrate significant angiogenic properties against negative controls. The co-culture of MDA231 cells and breast fibroblasts attracts a significantly better blood supply than MDA231 cells alone, unlike the MCF-7 cells. The precise role of MMPs in this tumour stroma interaction needs further investigation and raises the possibility that inhibition of MMP function could have a dual role in delaying tumour progression *in vivo*.

Analysis of the survival advantage to specialist treatment of breast cancer

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Background Before screening, treatment by a specialist was reported to confer a survival advantage. The aim of this study was to investigate whether the survival advantage persisted with longer follow-up and to determine if it could be explained by adjuvant therapy.

Methods All 5625 cases of invasive breast cancer in a defined geographical area from 1980 to 1994 were identified and the original pathology reports obtained. Cause of death was obtained from the Registrar General. The survival of women treated by a specialist was compared with that of women treated by non-specialists using Cox's proportional hazards model.

Results Survival in all groups treated by the specialist unit was significantly better, except in those with tumours greater than 40 mm (*Table*). In node-positive women, the survival advantage seen was greater in women aged 50–74 years than in those aged less than 50 years.

	Specialist		Non-specialist			
	5 years*	10 years*	5 years*	10 years*	Relative hazard ratio	*P*
Tumour size (mm)						
0–19	90	81	81	70	0·57 (0·41–0·80)	< 0·001
20–39	75	59	68	52	0·78 (0·63–0·96)	0·02
40 +	52	37	50	36	0·93 (0·71–1·20)	n.s.
Nodal status						
Negative	88	79	84	72	0·76 (0·58–0·99)	0·047
Positive	66	50	54	37	0·68 (0·56–0·81)	< 0·001
Age of node-positive women (years)						
< 50	65	47	54	41	0·72 (0·51–1·00)	n.s.
50–74	67	51	54	35	0·66 (0·53–0·82)	< 0·001

*Values are survival rates (%). Values in parentheses are 95 per cent confidence intervals. n.s., Not significant

Conclusion The survival advantage associated with specialist treatment persists and indicates a higher cure rate. This advantage exceeds any benefit from adjuvant therapy and is seen in women who would not be eligible for chemotherapy.

Expression of thrombospondin 1 in invasive breast cancer: its association with p53 status, angiogenesis and clinical outcome

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Background Angiogenesis is an important process in tumour progression. Thrombospondin 1 (TSP-1), an extracellular matrix glycoprotein, has been shown to have antiangiogenic properties. However, some studies have demonstrated an inhibitory role. Recent studies have shown an inverse relationship between TSP-1 expression and p53 status in cultured fibroblasts. The significance of this and its relevance to clinical outcome in invasive breast cancer is poorly understood. The role of TSP-1 expression, p53 status and microvessel density as a measure of angiogenesis has been examined in invasive breast cancer.

Methods Formalin-fixed paraffin-embedded tissue sections from 48 consecutive invasive breast cancers were examined immunohistochemically for TSP-1 and p53 expression. Microvessel density was estimated using CD31 endothelial cell antibody. The findings were correlated with recurrence-free and overall survival.

Results There was a significant correlation between TSP-1 expression and microvessel density ($P < 0\cdot03$) with high levels of TSP-1 expression found in conjunction with low microvessel density counts. High microvessel density was correlated with p53 positivity ($P < 0\cdot01$) and both microvessel density and p53 positivity were significantly correlated with recurrence-free survival and overall survival ($P < 0\cdot03$). However, TSP-1 expression was not significantly associated with recurrence-free or overall survival and there was only a loose non-significant inverse relationship between TSP-1 expression and p53 status.

Conclusion These results support the concept that TSP-1 expression has an antiangiogenic role in invasive breast cancer. These data also confirm that tumour microvessel density and p53-positive status are markers of poor clinical outcome. However, TSP-1 expression does not afford a survival advantage in invasive breast cancer nor does it exhibit an inverse relationship with p53 status.

Surgical introduction of endotoxin increases metastatic growth and circulating levels of vascular endothelial growth factor

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Background Surgical resection of primary tumours may paradoxically induce rapid growth of distant metastases through an angiogenic mechanism. Wound factors are usually regarded as the stimulus for vessel growth; however, these appear late in the circulation. It was hypothesized that endotoxin lipopolysaccharide (LPS) introduced at the time of surgery stimulates immune and tumour cell production of vascular endothelial growth factor (VEGF), a potent angiogenic factor, contributing to increased growth of metastases.

Methods Fifty Balb/c mice were injected with 1×10^5 4T1 mammary adenocarcinoma cells by tail-vein injection. On day 14 the animals received either anaesthesia alone, laparoscopy with carbon dioxide, laparoscopy with air, laparotomy, saline injection or LPS injection ($10\,\mu\text{m ml}^{-1}$). On day 5 following surgery or injection, lungs were excised and weighed as an indication of metastatic burden. Serum VEGF was assayed by enzyme-linked immunosorbent assay.

Results There was a significant increase in metastatic burden between the air laparoscopy and laparotomy groups compared with either controls or the carbon dioxide laparoscopy group. Similarly, metastatic burden was increased in the endotoxin group compared with saline controls. Mitotic index within the metastases and serum VEGF levels were significantly higher following endotoxin injection and either laparotomy or air laparoscopy compared with the appropriate controls.

Group ($n = 8$)	Metastatic burden	Mitotic index	Serum VEGF (pg ml^{-1})
Control (anaesthesia)	1·32(0·12)	4·39(0·63)	14·28(5·44)
Carbon dioxide laparoscopy	1·94(0·42)	4·71(0·15)	28·41(13·70)
Air laparoscopy	2·73(0·12)*	7·99(0·09)*	61·97(7·14)*
Laparotomy	3·37(0·14)*	8·33(0·21)*	77·92(5·00)*
Saline	1·99(0·10)	4·74(1·71)	33·88(7·34)
Endotoxin (10 μg ml^{-1})	2·84(0·20)†	7·68(0·42)†	207·85(42·74)†

Values are mean(s.d.). *$P < 0\cdot0001$ *versus* anaesthesia control; †$P < 0\cdot0003$, ‡$P < 0\cdot05$ *versus* saline.

Conclusion Open surgery induced higher rates of metastatic growth and raised levels of circulating VEGF compared with controls. Air laparoscopy and endotoxin injection led to a similar effect, with no significant effect observed when the peritoneum was sufflated with sterile carbon dioxide. This indicates that endotoxin introduced during open surgery may increase both tumour growth and angiogenesis. Therefore by reducing surgical exposure to LPS it may be possible to attenuate postoperative metastatic tumour growth.

Human tumour-derived endothelial cells exhibit decreased expression of Bcl-2 and Bag-1 and are more susceptible to interferon γ-induced apoptosis and antiangiogenesis

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Background Solid tumour growth and metastasis are dependent on the formation of new blood vessels (angiogenesis). Studies based on intact vessels or established cell lines have shown that tumour and normal blood vessels differ in their permeability and composition of the basement membrane. However, further investigation of these differences with potential significance for innovative therapeutics of tumour vascular targeting have been hindered because of the lack of readily available and purified human tumour-derived endothelial cells (HTDECs) for analysis. This study was carried out to establish the technique for isolation and identification of HTDECs and normal human vascular endothelial cells (HVECs).

Methods HTDECs were freshly isolated from human colorectal tumours ($n=5$) using collagenase and DNAase digestion, and Percoll gradient sedimentation. HTDECs were identified and confirmed by their angiotensin-converting enzyme activity, positivity for von Willebrand factor-related antigen staining, and typical capillary-like formation on Matrigel. HVECs were isolated from human umbilical veins ($n=6$). The expression of adhesion molecules on HTDECs and HVECs was assessed by flow cytometry. Expression of antiapoptotic gene proteins, Bcl-2 and Bag-1, was detected by Western immunoblotting. HTDEC and HVEC proliferation, capillary tube formation and apoptosis were also evaluated.

Results Both HTDECs and HVECs had similar expression of PECAM-1. However, HTDECs expressed high levels of intercellular adhesion molecule 1 (ICAM-1) and E-selectin compared with HVECs ($P<0{\cdot}05$). P-selectin was absent in normal HVECs, but was detected in HTDECs. As a result, the spontaneous adhesion of human lymphocytes to HTDECs was higher than to HVECs (27 *versus* 16 per cent, $P<0{\cdot}05$). Treatment of HTDECs with interferon (IFN) γ 250 units ml^{-1} for 24 h resulted in significant increases in inhibition of cell proliferation (72 per cent inhibition of control) and in cell apoptosis (31 per cent) compared with IFN-γ-treated HVECs (proliferation 38 per cent inhibition of control; apoptosis 15 per cent). IFN-γ markedly inhibited HTDEC capillary tube formation on Matrigel. Western blotting revealed that HTDECs expressed lower levels of Bcl-2 and Bag-1 gene proteins than normal HVECs.

Conclusion These studies confirm firstly the upregulation of ICAM-1 on HTDECs and the consequent increased lymphocyte adherence. The observations of decreased antiapoptotic gene protein, bcl-2 and bag-1 expression, and the associated increase in IFN-γ-induced apoptosis and antiangiogenesis in HTDECs may have implications for the design of new anticancer therapies.

Lipopolysaccharide-mediated upregulation of vascular endothelial growth factor in macrophages and tumour cells

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Background Angiogenesis is an important determinant of tumour proliferation and vascular endothelial growth factor (VEGF) is the most potent angiogenic factor known. The authors have shown that exposure to airborne endotoxin (lipopolysaccharide (LPS)) during surgery results in increased serum VEGF levels in a tumour-bearing murine model. The aim of this study was to determine the source of VEGF following macrophage and tumour cell exposure to LPS.

Methods Peritoneal macrophages isolated from LPS-sensitive (HEN) and LPS-resistant (HEJ) mice were adhered and stimulated *in vitro* with LPS (1–100 ng) for 24 h. Murine 4T1 mammary adenocarcinoma cells were cultured similarly. Human monocytes were isolated, matured to macrophages *in vitro* and activated with interferon γ before incubation with LPS 1–100 ng for 24 h. VEGF messenger RNA (mRNA) expression was determined semiquantitatively by reverse transcriptase–polymerase chain reaction and VEGF protein levels were determined by enzyme-linked immunosorbent assay.

Results VEGF mRNA and protein expression were not significantly altered in LPS-stimulated peritoneal macrophages isolated from LPS-sensitive or LPS-resistant mice. Human macrophage VEGF mRNA expression was increased in response to LPS in a dose-dependent manner. Mammary carcinoma cell production of VEGF following LPS stimulation was upregulated.

Conclusion In the murine model, LPS upregulates VEGF production by tumour cells but not by macrophages. In contrast, human macrophages increase VEGF production following LPS exposure. This may reflect the differential expression of CD14 LPS receptor between human (positive) and murine (negative) macrophages. Perioperative exposure to LPS may stimulate angiogenesis following surgery generating a permissive environment for tumour growth.

Omeprazole-induced hypergastrinaemia promotes the progression of adenomas and decreases survival in the *Min* mouse model of familial adenomatous polyposis

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Background Gastrin is a potent mitogen for colorectal epithelium and tumours. Overexpression of the gastrin receptor has been shown in hyperproliferative colonic epithelium and all grades of adenomas. Thus a state of hypergastrinaemia may promote progression through the adenoma–carcinoma sequence. The effect of omeprazole-induced hypergastrinaemia on the progression of intestinal neoplasia was determined in the *Min* (multiple intestinal neoplasia) mouse model of polyposis coli.

Methods Mice were entered into the study when polymerase chain reaction analysis confirmed the Min^{+} genotype. *Min* mice were randomized into four groups to receive: omeprazole (75 mg kg^{-1} daily oral treatment); omeprazole + Gastrimmune (a gastrin immunogen inducing the *in situ* formation of antigastrin antibodies, 100 μg per mouse on day 0 and every 3 weeks); control mice received oral vehicle control with or without a control immunogen. Serum gastrin levels were measured by radioimmunoassay. Before termination, 5-bromo-2′-deoxyuridine was administered to generate a proliferative index.

Results Treatment with omeprazole produced serum gastrin levels of 236 pg ml^{-1} compared with 67 pg ml^{-1} in the untreated group. Hypergastrinaemia significantly decreased survival compared with the appropriate control ($P=0{\cdot}0001$, log rank test), with mice in the control group having a 50 per cent survival of 9·5 weeks compared with 6 weeks in the omeprazole group. Gastrimmune induced the formation of serum antibodies with an antigen binding capacity of more than 20 ng ml^{-1} resulting in effective neutralization of the hypergastrinaemic state. Gastrin neutralization resulted in a reversal of the survival disadvantage induced by omeprazole ($P=0{\cdot}0017$). The hypergastrinaemic mice had enhanced proliferation of normal colonic mucosa (9·5 per cent proliferating cells increased to 20·1 per cent; $P<0{\cdot}05$, Mann–Whitney U test) and colonic neoplasia (22·3 per cent increased to 35·0 per cent, $P<0{\cdot}01$).

Conclusion The level of hypergastrinaemia was in the range attained in humans on a maintenance dose of omeprazole and resulted in enhanced progression through the adenoma–carcinoma sequence. Gastrin was confirmed as the mediator inducing a state of hyperproliferation within both normal and neoplastic colonic epithelium. This study highlights the need to reassess the safety of hypergastrinaemia.

Thermal preconditioning attenuates no-reflow phenomenon: an intravital microscopy study

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Background In previous studies, the authors have shown that induction of a 70-kDa heat-shock protein by thermal preconditioning (TP) attenuates microvascular injury caused by ischaemia–reperfusion (I–R). The most damaging consequence of prolonged I–R injury is the permanent occlusion of part or the whole of the microvasculature with resultant failure, the 'no reflow' phenomenon. The purpose of this study was to investigate the effect of TP on the postischaemic no-reflow phenomenon in postcapillary venules. No reflow is defined as the failure to observe forward flow in the mesenteric venule under intravital microscopic observation.

Methods Sprague–Dawley rats were randomized into an I–R group ($n = 15$) and TP + I–R group ($n = 14$). TP was induced by raising core body temperature to 41 ± 0·5°C for 15 min 18 h before I–R injury, which in turn was established by occlusion of the superior mesenteric and coeliac vascular pedicle for 30 min, followed by 60 min of reperfusion. Blood flow in a mesenteric postcapillary venule (22–35 μm) was measured by intravital microscopy. The mean systemic blood pressure (MSBP) was observed. Expression of the 70-kDa heat-shock protein was determined by Western immunoblotting.

Results Results are given for baseline (0 min), during ischaemia (I-30 min) and during reperfusion (R-10 and R-60 min).

	Blood flow (nl s^{-1})		MSBP (mmHg)	
	I–R	TP + I–R	I–R	TP + I–R
0 min	1·6(0·6)	2·0(0·5)	111·8(10·1)	109·7(8·7)
I-30 min	0·0(0·0)	0·0(0·0)	106·1(15·3)	103·7(15·5)
R-10 min	0·1(0·2)	0·6(0·4)*	74·7(16·6)	86·8(13·8)*
R-60 min	0·1(0·3)	0·7(0·7)*	71·4(15·9)	89·1(15·1)*

Values are mean(s.d.). *$P < 0·05$ (I–R *versus* TP + I–R, analysis of variance with Scheffe post hoc correction)

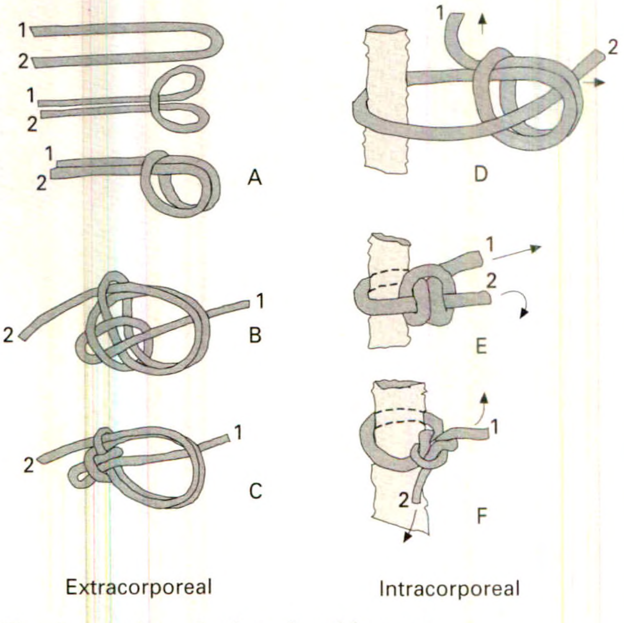
Occlusion of the vascular pedicle for 30 min resulted in the no-reflow phenomenon in 11 of 15 rats in the I–R group. This was associated with severe hypotension. Thermal preconditioning significantly reduced the incidence of no reflow (three of 14, $P < 0·05$). In addition, thermal preconditioning attenuated I–R-induced hypotension. This was associated with expression of the 70-kDa heat-shock protein.

Conclusion These data suggest that thermal preconditioning may be of value in treating the consequence of severe ischaemia.

Errata

J. A. Puñal Rodríguez. Reliable double-component knots for laparoscopic surgery. *Br J Surg* 1998; **85**: 19.

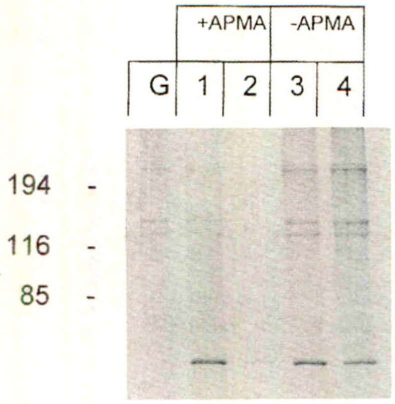
The correct version of *Fig. 1* is as follows:



The Journal apologizes for this error.

M. S. Ågren, L. N. Jorgensen, M. Andersen, J. Viljanto and F. Gottrup. Matrix metalloproteinase 9 level predicts optimal collagen deposition during early wound repair in humans. *Br J Surg* 1998; **85**: 68–71.

The correct version of *Fig. 2* is as follows:



The Friary Press apologize for this error.

British Journal of Surgery 1998, **85**, 716–717

Correspondence

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Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial

Sir

Kalfarentzos *et al.* are to be congratulated for demonstrating that enteral nutrition may be administered with safety to patients with severe pancreatitis (*Br J Surg* 1997; **84**: 1665–9), but some of their conclusions should be discussed.

Targets for energy and nitrogen delivery, related to body mass, were determined but the mean daily intakes achieved were below this. Actual energy delivery was only three-quarters of that intended and no explanation was given. If feed reformulation would have allowed more complete nutrition by one route over another, the discrepancy might be of significance. Some patients developed diarrhoea, but it is unclear whether this was a consequence of the route of feeding and if the manner of feed delivery therefore was changed. Maintenance of nutritional status was the central aim of the study and was inferred from urinary nitrogen balance studies. In patients with severe pancreatitis substantial nitrogen loss occurs in the acute-phase response and as a consequence of pancreatic necrosis and its resection. Assessment of urinary nitrogen loss alone would seem insufficient to determine whole-body balance in this context. The authors stated that enteral and parenteral nutrition were equally effective to maintain lean body mass, but provided no evidence to support this. Body composition was not directly measured. It was implied that, because urinary nitrogen balance was similar in the two groups, lean body mass must have been similarly preserved; this is a bold assumption. Deduction of change in body composition from nitrogen balance is only possible when assessment of balance is complete and initial body composition is known[1]. No data regarding the nutritional status of the patients at inclusion in the study were provided. Accurate measurement of body composition in critically ill patients may be impossible because of practical limitations but muscle function is related to lean body mass and improved function may precede restoration of lean body mass when nutritional support is provided[2]. Non-dominant hand grip strength or FEV_1 (forced expiratory volume in 1 s) could perhaps have been assessed during the study.

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1 King RFGJ, McMahon MJ, Burkinshaw L, Laughland A, Almond DJ, Yeung CK *et al.* A comparison of changes in body nitrogen measured by *in vivo* neutron activation analysis and urinary nitrogen balance. *Clin Nutr* 1988; 7: 231–6.
2 Hill GL. Impact of nutritional support on the clinical outcome of the surgical patient. *Clin Nutr* 1994; **13**: 331–40.

Author's reply

Sir

We thank Mr Everitt for his comments on our study and will respond briefly to each point.

First, regarding target values for energy and nitrogen delivery *versus* actual values, we wish to point out that target values are expressed as total kcal per kg per day (Patients and methods: Randomization and nutrition methods) whereas actual energy delivery is expressed as non-protein kcal per kg per day (Results: Tolerance and nutrition data). The actual delivery, if expressed as total kcal per kg per day, is 29–30 and therefore not significantly different from target values. Protein delivery was also comparable to target value (1·43–1·45 g per kg per day *versus* minimum target value of 1·5 g per kg per day).

The incidence of diarrhoea was not significantly different between groups; we considered that this did not depend on the route of feeding, but rather on other factors. Neither the manner of feed delivery (continuous 24 h infusion in all patients) nor the rate of infusion were changed for this reason in any patient during the course of the study.

Finally, we agree that the use of nitrogen balance alone may not be the best way to determine lean body mass. However, this was the best method available to us at the time. We have no means of directly measuring body composition that would not only have been very expensive but, as Mr Everitt himself points out, extremely difficult if not impossible to perform accurately in these critically ill patients. Non-dominant hand grip strength and FEV_1 would have been equally difficult to assess.

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Randomized controlled trial of open and closed haemorrhoidectomy

Sir

I read with interest the article by Ho *et al.* (*Br J Surg* 1997; **84**: 1729–30). We have been performing closed haemorrhoidectomy with local anaesthesia[1] for over 30 years and find the paper's conclusion unacceptable and the reported complication rate high.

The technique of closed haemorrhoidectomy described by the authors is not as performed by most surgeons in the USA and not as originally described by Ferguson and Heaton[2].

Diathermy deters from primary healing by first intention. Including small bites of internal sphincter during closure contributes to dehiscence by pulling away the approximated edges following inevitable sphincter contraction. A previous large series showed secondary haemorrhage in 14 of 2274 patients. Only five patients developed infection[3]. A postoperative bleeding rate of 6 per cent following open haemorrhoidectomy and 9 per cent following closed haemorrhoidectomy is unacceptably high. Faecal impaction following open haemorrhoidectomy can be avoided by administering an appropriate laxative.

The authors suggest that it is arguable whether the wound dehiscence rate of eight of 33 following closed haemorrhoidectomy would be less if fewer than three haemorrhoids were excised. It is our practice to remove three or more haemorrhoids and the haemorrhoidal tissue excised should allow for approximation of the cut edges without tension.

A comparison of the techniques is only valid if they are performed appropriately.

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1 Khubchandani IT. Operative hemorrhoidectomy. *Techniques of Colorectal Surgery. The Surgical Clinics of North America.* Philadelphia, Pennsylvania: W B Saunders, 1988: 1411–16.

2 Ferguson JA, Heaton JR. Closed hemorrhoidectomy. *Dis Colon Rectum* 1959; **2**: 176–9.
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Authors' reply

Sir
We are pleased that our paper stimulated the interest of Dr Khubchandani. We can understand his hesitancy over the use of diathermy, based on his retrospective experience. None the less, prospective controlled randomized data have shown that, with proper use, this technique was at least as safe as conventional scissors[1]. Furthermore, our wound dehiscence rate after closed haemorrhoidectomy (observed with strict prospective methodology) was not more than that previously reported in another controlled randomized study[2]. A comparison of results is only valid if the study methodologies and quality of data are equivalent.

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1 Seow-Choen F, Ho YH, Ang HG, Goh HS. Prospective, randomized trial comparing pain and clinical function after conventional scissors excision/ligation *vs.* diathermy excision without ligation of symptomatic prolapsed haemorrhoids. *Dis Colon Rectum* 1992; **35**: 1165–9.
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Comparison of endoanal magnetic resonance imaging with surgical findings in perirectal sepsis

Sir
We enjoyed the article by Abar *et al.* relating to magnetic resonance imaging (MRI) of perirectal sepsis (*Br J Surg* 1998; **85**: 111–14), which again demonstrates the value of this technique for preoperative assessment. The authors chose to use an endoanal receiver coil, which increases spatial resolution in exchange for a limited field-of-view, and correctly state that disease lying beyond this will be undetectable. Indeed, failure to visualize a low fistula in one patient, and a supralevator collection with attendant extrasphincteric track in another, were blamed on this. This phenomenon is analogous to that encountered with anal endosonography, which may also miss disease beyond the focal range of the probe[1].

Initial reports of MRI in cryptoglandular fistula disease used a body coil[2], which does not suffer this disadvantage. Although spatial resolution is reduced and the separate components of the sphincter complex are not as well visualized, this does not seem to hinder fistula classification. Studies using body coils have achieved surgical concordance approaching 100 per cent[3,4]. We have recently completed a prospective comparison of a prototype endoanal coil (Philips Medical Systems, London, UK) and conventional body coil imaging in 30 subjects with complex cryptoglandular disease[5]. Surgical concordance for body coil imaging reached 96 per cent while endoanal imaging could only achieve 68 per cent due to field-of-view limitations similar to those cited by Zbar *et al.* Additionally, anal pain prevented coil insertion in five patients. Complex fistula disease is characterized by remote tracks and collections, intuitively suggesting that body coil examination may be preferable. To our knowledge, dedicated endoanal coils are not yet commercially available despite initial reports 3 years ago[6].

We do not want to devalue endoanal coils but fistula imaging is possible on the majority of commercially available MRI scanners without resorting to such equipment. Ultimately, examination employing both coils is likely to be the gold standard. We reserve endoanal imaging for 'troubleshooting' but radiological unfamiliarity with fistula classification far outweighs any difference between techniques.

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1 Choen S, Burnett S, Bartram CI *et al.* Comparison between anal endosonography and digital examination in the evaluation of anal fistulae. *Br J Surg* 1991; **78**: 445–7.
2 Lunniss PJ, Armstrong P, Barker PG *et al.* Magnetic resonance imaging of anal fistulae. *Lancet* 1992; **340**: 394–6.
3 Lunniss PJ, Barker PG, Sultan AH *et al.* Magnetic resonance imaging of fistula-*in-ano*. *Dis Colon Rectum* 1994; **37**: 708–18.
4 Beckingham IJ, Spencer JA, Ward J *et al.* Prospective evaluation of dynamic contrast enhanced magnetic resonance imaging in the evaluation of fistula-*in-ano*. *Br J Surg* 1996; **83**: 1396–8.
5 Halligan S, Bartram CI. MR imaging of fistula-*in-ano*: are endoanal coils the gold standard? *AJR Am J Roentgenol* 1998; (in press).
6 de Souza NM, Puni R, Kmiot WA, Bartram CI, Hall AS, Bydder GM. MRI of the anal sphincter. *J Comput Assist Tomogr* 1995; **19**: 745–51.

Book reviews

Critical Care of the Surgical Patient. Companion Series to Bailey and Love's Short Practice of Surgery

G. C. Hanson (ed.). 282 × 223 mm. Pp. 454. Illustrated. 1997. New York: Chapman and Hall. Price not supplied.

Intensive care is an essential component of surgical practice. The advent of the intensivist has too often resulted in the surgical team being relegated to a back seat in the management of patients. It is, therefore, appropriate that a group of intensivists and enthusiasts from other disciplines, including surgery, have come together and written a very authoritative and readable text encouraging a team approach to the management of patients in the intensive therapy unit. At 450 pages in length with some heavy duty physics, this is not a book for light bedtime reading, but it is both informative and authoritative. I am sure that this volume will be useful for higher surgical trainees preparing for the intercollegiate examination as well as surgeons updating their knowledge or needing a reference book of intensive care practice. The text is comprehensive in its coverage, with sections on the management of intensive care equipment, and on the staffing and nursing of an intensive care unit. At the other end of the spectrum, the important ethical issues surrounding the management of critically ill patients are covered in some detail. The book is well illustrated and referenced. I would recommend this volume to all with an interest in the management of patients in intensive care. It should enable the surgeon to hold his own in discussion with the intensivist.

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Complications of Endoscopic and Laparoscopic Surgery: Prevention and Management

J. L. Ponsky (ed.). 285 × 220 mm. Pp. 292. Illustrated. 1997. Philadelphia, Pennsylvania: Lippincott-Raven. £95.50.

This book is a multiauthor text which states in its preface that its aim is to compile the complications of endoscopic and laparoscopic surgery, and to describe their prevention and management. It has 39 contributing authors and their styles are markedly different. Some of the chapters fulfil the overall aim of the book; other chapters are devoted almost entirely to descriptions of technique and some devote pages to the indications for procedures. Descriptions of procedures and their indications can be found in established texts on endoscopic and laparoscopic surgery. The subject of the book is of topical interest with the expansion of endoscopic and laparoscopic surgery, the increasing numbers of complications reported and their malpractice implications. The authors have covered the full spectrum of endoscopic and laparoscopic surgery. Many of the authors are well known in their field. I believe that postgraduate specialists would prefer a more detailed bibliography at the end of each chapter. The book would be improved if the authors itemized in the text specific references to support their quotation of various percentage complications. The text is written entirely from an American perspective and much of the terminology and abbreviations are USA orientated. Chapter 10 is out of style with the rest of the chapters in that it is almost a mini-paper. Chapter 11 is good, although incidences of abdominal wall hernia after surgery should be referenced. Chapter 26 is useful but the illustrations could be greatly improved. Overall, there is a place for this text. However, it is unlikely to be purchased by individual postgraduate trainees or by many general surgeons, although it will appeal to specialized endoscopic surgeons. It would be a useful text for libraries.

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Hamilton Bailey's Physical Signs. Demonstrations of Physical Signs in Clinical Surgery. 18th ed.

J. S. P. Lumley (ed.). 245 × 188 mm. Pp. 518. Illustrated. 1997. Oxford: Butterworth-Heinemann. £39.50.

Since its first edition in 1927 this book has been a standard text for both undergraduates and postgraduates. This latest edition is the most radical revision that has been undertaken during those 70 years, containing 40 chapters written by 14 authors. It has a comprehensive index and has been redesigned with more than 1000 new full-colour photographs. There are new chapters on multiple injury, tropical disease and AIDS. Inevitably, this has meant change that not all will appreciate. Although old and black and white, some previous illustrations were classics of their time and I do mourn the passing of the foonotes which I consider imparted useful information.

The content of the chapters varies. The one on breast disease itemizes staging by the International and tumour node metastasis classifications, but such classification is lacking for other tumours. Some authors have gone beyond the demonstration of physical signs, discussing presentation, pathology, prognosis and even giving brief outlines of treatment. When this has occurred, to remain compact, the account has been dogmatic with little discussion of alternative views. In an era of increasing specialization, this can be disadvantageous and it would be safer to adhere strictly to the original concept of the demonstration of physical signs. I received this volume 2 weeks before examining for the AFRCS (Ed) and, during the clinical examinations, it crossed my mind several times that a number of candidates would have done well to have read this book beforehand. Professor Lumley and his coauthors are to be congratulated on ensuring that this tried and tested work will have a secure future in the next millennium.

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Interpretation

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The Association of Surgeons of Great Britain and Ireland, jointly with the **British Journal of Surgery Society**, are offering £10,000 per annum to sponsor surgeons wishing to work on a short term basis, primarily in the Third World. The purpose of this Scheme is to provide training and support for overseas medical schools in the development of their undergraduate and postgraduate training programmes and also for research, thereby, establishing links with these centres.

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Association of Surgeons of Great Britain and Ireland

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Association of Surgeons of Great Britain and Ireland

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Association of Surgeons of Great Britain and Ireland

The British Journal of Surgery is pleased again to have the opportunity of publishing the abstracts of the work presented at the Annual Scientific Meeting of the Association of Surgeons of Great Britain and Ireland. The pages which follow contain 317 abstracts, selected from a bumper total of 577 submitted, a fine testament to the health and vigour of scientific surgery within these islands.

The whole of general surgery is represented, with oral presentations on the following topics: vascular 55, coloproctology 33, general 31, upper gastrointestinal 24, breast 24, hepatobiliary & pancreatic 18, transplant/endocrine 9, and 7 abstracts for the Moynihan Prize session. In addition, there are 116 abstracts of poster presentations.

The October 1998 issue of the *British Journal of Surgery* will contain full papers describing work first presented at the Annual Scientific Meeting of the Association in Edinburgh this year. These papers will be selected after peer review from manuscripts submitted from Fellows and their guests. The authors of the paper adjudged best will receive the Association's *BJS* Prize.

Both this supplement and the October issue of the Journal cement a long-term relationship between the *BJS* and the Association. Over the years this relationship has benefited both organizations and we believe that it will continue. In the meantime, the Editors hope you will find the present publication attractive and worthy of retention on your bookshelves. On behalf of my colleagues at the *BJS*, I wish all participants an enjoyable congress in Edinburgh.

John Murie
Joint Editor, BJS

Moynihan 1–7

Thursday 14 May, 08·30–10·30

Moynihan 001

The quantification of normal anal canal anatomy and sphincter defects using three-dimensional endoanal sonography

D.M. Gold, C.I. Bartram, S. Halligan, M.A. Kamm and W.A. Kmiot *Department of Surgery, Hammersmith Hospital, Du Cane Road, London, and Departments of Radiology and Physiology, St Mark's Hospital, Northwick Park, Harrow, Middlesex*

Background: Conventional anal ultrasound provides no information on sphincter anatomy in the longitudinal plane. Using three-dimensional endoanal ultrasound we have studied whether longitudinal differences exist between normal male and female anal sphincters and explored the potential relationship between radial degree of a sphincter defect and its length.
Method: Twenty normal subjects and 24 faecally incontinent patients (25 external and five internal sphincter defects) underwent scanning and reconstruction to produce sagittal and coronal images of the anal sphincters to facilitate measurement. The radial degree of each sphincter defect was related to its longitudinal extent.
Results: The male anal canal was longer than in the female: $32{\cdot}6\pm5{\cdot}3$* mm compared with $25{\cdot}1\pm3{\cdot}4$* mm, $P<0{\cdot}001$**. The male internal anal sphincter (IAS) was longer than the female: $25{\cdot}6\pm6{\cdot}3$* mm and $19{\cdot}8\pm4{\cdot}0$* mm, respectively, $P<0{\cdot}02$**. However, mean IAS length as a percentage of total anal canal length was not different; 78·3 per cent ± 8·2 per cent* and 78·7 per cent ± 9·0 per cent*, respectively, $P<0{\cdot}91$**. The male anterior external anal sphincter (EAS) was longer than the female; $32{\cdot}6\pm5{\cdot}3$* mm and $15{\cdot}3\pm2{\cdot}8$* mm, respectively, $P<0{\cdot}0001$**; as was the anterior EAS as a percentage ratio of total anal canal length 100 per cent (100 per cent–100 per cent)§ and 62·9 per cent (53·8–70·7 per cent)§, respectively, $P<0{\cdot}0001$§§. The radial angle of sphincter defect related to length for the 25 EAS and the five IAS defects gave R^2 values of >80·0 per cent. $P<0{\cdot}0001$ for both.†
Conclusion: These data explain why certain women are predisposed to faecal incontinence after seemingly trivial obstetric or surgical trauma.
* = standard deviation; ** = unpaired *t* test; § = median and interquartile range; §§ = Mann–Whitney U-test; † = analysis of variances.

Moynihan 002

Metabolic consequences of radical curative resection for gastric cancer: total vs subtotal gastrectomy

G.V. Miller, J.B. Davies, S.M. Young, G. Young, D. Johnston and H.M. Sue Ling *Department of Surgery and Centre for Digestive Diseases, Leeds General Infirmary, Leeds*

Background: Subtotal gastrectomy for gastric cancer is reputed to be a safer alternative to total gastrectomy 'en principe' and is suggested to afford a better long-term nutritional outcome because of the presence of the small gastric remnant. We assessed the long-term nutritional outcome of patients after subtotal or total gastrectomy for gastric cancer to test this hypothesis.
Method: Fifty patients with no evidence of recurrent disease were recalled for assessment 5–15 years after curative resection for gastric cancer. Biochemical and anthropometric variables were measured in these patients and compared with data from 30 age- and sex-matched control subjects.
Results: The table below indicates median (interquartile range) values for each variable. Comparison between subgroups (control, total and subtotal gastrectomy) by sex was assessed using the Mann–Whitney U test.

	Control subjects		Total gastrectomy		Subtotal gastrectomy	
	M ($n=21$)	F ($n=9$)	M ($n=26$)	F ($n=7$)	M ($n=11$)	F ($n=7$)
Weight (kg)	71·4 (16)	64 (18·2)	62 (9·5)	49·4 (5·4)	63 (23·9)	46 (21)
Recall weight	—	—	73 (12·9)	59 (21)	77·6 (6·5)	60·3 (21)
BMI (kg/m^2)	24·7 (3·7)	24·7 (4)	22·1 (4·9)	21·6 (2·1)	21·8 (6·9)	17·5 (9·2)
Recall BMI	—	—	25·8 (4·1)	25·7 (3·4)	26·3 (3·9)	25·1 (9·7)
Per cent fat	22·2 (4·7)	37·7 (4·1)	18·6 (11)	26·9 (10)	16·1 (12)	21·4 (19)
Albumin (g/L)	37·1 (4·2)	38·2 (1·5)	36·2 (4·9)	37·9 (4·8)	35·2 (4·6)	34·6 (7·6)
Prealbumin (g/L)	22·9 (6·7)	23 (2·2)	20·1 (7·5)	17·4 (9·7)	19·1 (6·6)	19·8 (3·9)
CRP (mg/L)	0.64 (0·9)	0·55 (0·4)	0·56 (0·9)	0·61 (0·6)	1.1 (1.1)	0·76 (1·1)
Transferrin (mg/dL)	314 (59)	276 (98)	319 (87)	306 (184)	290 (139)	285 (112)

M = male; F = female; BMI = body mass index; CRP = C reactive protein.

Current weight and BMI were significantly lower than recall values for all patients after gastric resection, and significantly lower than controls. However, there was no significant difference in nutritional variables between patients undergoing total gastrectomy and subtotal gastrectomy or in control subjects.
Conclusion: The choice of surgical resection for gastric cancer should be dictated by tumour location, extent and oncological safety, and performed by suitably experienced surgeons, as long-term nutritional status is maintained at similar levels to control subjects, irrespective of type of resection.

Moynihan 003

A comparison of TGF β mRNA levels in renal transplant biopsies from patients immunosuppressed with cyclosporin or FK506

S.T. Williams, G.R. Bicknell*, P.N. Furness* and M.L. Nicholson *Departments of Surgery and *Pathology, Leicester General Hospital, Leicester*

Aims: TGF β, a fibrogenic cytokine thought to have an important role in the development of chronic allograft fibrosis following renal transplantation, may be upregulated by immunosuppression with cyclosporin. The aim of this study was to compare early TGF β gene expression in renal transplant recipients immunosuppressed with either cyclosporin or the new immunosuppressive agent tacrolimus (FK506).
Method: Renal transplant recipients received either Neoral cyclosporin 15 mg/kg/day ($n=19$) or tacrolimus 0·2 mg/kg/day ($n=19$). Tissue core transplant biopsies were performed 1 week, and 3, 6 and 12 months post-transplant. Single glomeruli were plucked from the surface of transplant biopsies and total mRNA was extracted using oligo DT dynabeads. Complementary DNA was synthesized by reverse transcription and the polymerase chain reaction (PCR) was used to amplify specific mRNA species. PCR products were quantified using an ELISA method and levels compared to the expression of a housekeeping gene. One hundred and eighty biopsies were analysed for the mRNA of TGF β, collagen type III, collagen IV (alpha 2 chain), tenascin, matrix metalloproteinase MMP2 and its inhibitors TIMP1 and TIMP2.
Results: TGF β expression correlated with collagen III ($r=0{\cdot}18$, $P=0{\cdot}015$), collagen IV alpha 2 ($r=0{\cdot}35$, $P<0{\cdot}1$), tenascin ($r=0{\cdot}73$, $P<0{\cdot}01$), TIMP1 ($r=0{\cdot}61$, $P<0{\cdot}01$) and TIMP2 ($r=0{\cdot}57$, $P<0{\cdot}01$), suggesting that TGF β is a fibrogenic influence in human renal transplants. However, there were no differences in the levels of mRNA for TGF β between recipients treated with cyclosporin (mean ± SEM = 0·09 u) and those treated with tacrolimus (mean ± SEM = 0·27 ± 0·06 u) ($P=0{\cdot}23$). In addition the whole blood levels of cyclosporin or tacrolimus did not correlate with mRNA levels of TGF β.

Conclusion: The technique described is a valuable tool in the investigation of early molecular events following renal transplantation. In this study there was no evidence for differences in the early expression of the gene for the profibrotic cytokine TGFβ between patients treated with cyclosporin or tacrolimus.

Moynihan 004

Marimastat inhibits neointimal thickening in a model of human vein graft stenosis

I.M. Loftus, K. Porter, M. Peterson, P.R.F. Bell, N.J.M. London and M.M. Thompson *Department of Surgery, University of Leicester, Leicester*

Background: Matrix metalloproteinases (MMPs) have been implicated in the development of vein graft stenosis, a process characterized by extensive remodelling and accumulation of the extracellular matrix. This study investigated whether marimastat (a non-specific MMP inhibitor) prevented myointimal hyperplasia in cultured human long saphenous vein.
Method: Eight segments of human vein were cultured in medium supplemented with therapeutic and supra-therapeutic doses of marimastat. Following 14 days of organ culture, one half of the tissue was homogenized and dialysed to extract MMPs, whilst the other half was prepared for histology. Neointimal thickness was measured by stereological analysis. Quantification of MMP2 and MMP9 was performed by gel enzymography.
Results: Neointimal thickness was significantly reduced in vein cultured with marimastat at 10^{-5} and 10^{-6}M concentrations when compared to control segments. Levels of MMP2 and MMP9 were significantly lower in vein cultured with marimastat at both concentrations. These results are summarized as follows (enzymography results shown as ratio to a control):

	Marimastat concentration			
	Control	10^{-5}M	10^{-6}M	*P* value
Neointimal thickness median (range) μm	22 (17–29)	4·5 (0–8)	7 (0–14)	$P<0·02$
MMP9	1·08 (0·57–1·57)	0·68 (0·37–0·91)	0·70 (0·47–0·96)	$P<0·05$
MMP2	1·18 (0·79–1·73)	0·67 (0·36–0·86)	0·81 (0·54–1·40)	$P<0·001$

Conclusion: Marimastat significantly reduced the level of MMF2 and MMP9 in this model of vein graft stenosis. This was accompanied by a significant reduction in neointimal thickening. Inhibition of MMPs therefore offers a pathway for pharmacotherapy to prevent vein graft stenosis *in vivo*.

Moynihan 005

Pathophysiology of postoperative lower limb compartment syndrome following prolonged pelvic surgery

A.F. Horgan, S.M. Geddes and I.G. Finlay *Department of Coloproctology, Glasgow Royal Infirmary University NHS Trust, Glasgow*

Background: Lower limb compartment syndrome (LLCS) is a rare, but devastating complication of prolonged pelvic surgery with little scientific information available regarding its pathophysiology.
Method: We studied 12 patients who underwent prolonged pelvic colorectal procedures in order to determine the intraoperative risk factors for developing LLCS. Blood flow to the lower limbs was monitored before, during and after surgery, by means of intra-arterial dorsalis pedis cannulation, laser Doppler flowmetry to skin and muscle, pulse oximetry and clinical observation. Recordings were taken every 15 minutes and on any alteration of the patient's position. Degree of elevation of the legs and head-down tilt was recorded, as was systemic blood pressure at all times.
Results: Mean operative time was 210 min (180 to 320 min). Good correlation was noted between laser Doppler index at skin level and arterial pressure in the dorsalis pedis. Oxygen saturation, on the other hand, did not correlate well with the other indices and gave consistently high readings (>96 per cent) until pulsatile flow to the foot ceased completely. Positioning the patient's leg in the lithotomy position did not lead to a significant decrease in foot perfusion. Addition of the head-down tilt, however, led to a rapid decrease in limb perfusion ($P<0·05$), with no pulsatile flow demonstrable on arterial line tracing and Doppler skin perfusion flux approaching zero, with clinically apparent ischaemia of the foot. These observations occurred despite a systemic arterial systolic blood pressure of >100 mmHg. Muscle blood flow in the anterior tibial compartment, as measured by laser Doppler flowmetry, revealed a ten-fold increase in perfusion index ($P<0·01$), which peaked in the second hour postoperatively, and occurred in the absence of any significant increase in skin perfusion or dorsalis pedis arterial blood pressure.
Conclusion: These data confirm the hypothesis that LLCS occurs as a result of a reperfusion injury confined to the muscle compartments. We suggest that hypotensive anaesthesia and Trendelenburg position are the major risk factors for LLCS and should be used for as short a period as possible during prolonged pelvic surgery.

Moynihan 006

Tracking of labelled monocytes during resolution of venous thrombi reveals their active recruitment from the vein wall

C.L. McGuinness, J. Humphries, A. Smith and K.G. Burnand
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Background: Monocytes are present in large numbers in mature human thrombi. The origin of these cells and the stimulus for their infiltration are unknown but it is unlikely that they are passively trapped as they only represent a small percentage of circulating white cells. The aim of this study was to track monocytic cells and discover the route by which they enter a thrombus.
Method: Home Office approval was obtained. A rat model of thrombosis was used. Rat mononuclear cell preparations were labelled with a red fluorescent phagocytic cell marker (PKH26-PCL). 10^7-labelled cells were injected intravenously immediately prior to thrombus induction. Whole blood, inferior cava containing thrombus and specimens from other organs were harvested at 1 h, 1, 2, 3 and 4 days, and 1, 2 and 6 weeks. Multiple contiguous frozen sections were processed for fluorescence microscopy and immunohistochemistry using the rat monocyte marker, ED-1.
Results: Fluorescent monocytes were found in the circulation for up to 1 week after infusion and their numbers in the thrombus increased from <5 per section, observed between 1 h and 3 days, to >100 per section at 1 week ($P<0·005$). At 3 days, fluorescent cells could be seen within the vasa vasorum and the surrounding tissue of the inferior vena cava. The proportion of monocytes seen in other tissues increased with time, but most fluorescent tissue monocytes were found in the lung and spleen.
Conclusion: Monocytes are actively recruited into thrombus between 3 and 7 days after thrombus formation, and they appear to enter from the vasa vasorum and surrounding tissues rather than the circulating blood adjacent to the thrombus. As monocytes produce plasminogen activators, their migration may be important in thrombus resolution.

Moynihan 007

Gut barrier failure in patients with acute pancreatitis

B.J. Ammori, P.C. Leeder, R.F.G.J. King, I.G. Martin, M. Larvin and M.J. McMahon *Leeds Institute for Minimally Invasive Therapy, The General Infirmary, Leeds*

Background: The aim of this study was to determine if gut permeability, measured within the first 48 h of admission, is increased in patients with acute pancreatitis and whether this correlates with disease severity.
Method: Intestinal absorption and renal excretion of polyethylene glycol

(PEG) 400 (micromolecule) and PEG 3350 (macromolecule) was measured to determine gut permeability changes. PEG 400 (5 g) and PEG 3350 (40 g) were administered enterally. Their detection in urine was achieved using high performance liquid chromatography. Patients were classified as having 'mild' or 'severe' disease according to the definitions of the Atlanta International Symposium of 1992. APACHE-II scores and C-reactive protein (CRP) were also determined on admission. Fifty-two patients (36 mild, 16 severe) and 12 healthy subjects were studied.

Results: Gut permeability to both molecules was significantly increased in patients with severe disease compared with mild disease and healthy controls. There was no significant difference in gut permeability to either molecule between patients with mild disease and controls.

	No. patients	Age (mean)	APACHE-II (median)	CRP (mean)	PEG 400 % retrieved (median)	PEG 3350 % retrieved (median)
Severe	16	57·5	10	250	60·7**	0·46**
Mild	36	54	7·5	95	11·1*	0·04*
Control	12	54	—	—	26·3	0·12

**Severe vs mild or control ($P<0{\cdot}001$, χ^2-test); *Mild vs control 'not significant'.

Conclusion: Gut permeability is significantly impaired in patients with severe acute pancreatitis and at an early stage of the disease. Breakdown in gut barrier function may play an important role in the development of complications of acute pancreatitis.

Endocrine/Transplantation 001

Adrenal cortical tumours in childhood

C.P. Driver, J. Birch, D.C.S. Gough and J. Bruce *Royal Manchester Children's Hospital, Pendlebury, Manchester*

Background: This study aimed to review the experience of adrenocortical tumours in the North West of England.
Method: A retrospective analysis of 18 children with a diagnosis of an adrenal cortical tumour in the 41-year period between 1954 and 1995, identified from the Manchester Children's Tumour Registry.
Results: Fourteen children had a carcinoma and four had an adenoma. The majority of patients had clinical signs of endocrine dysfunction at presentation, with virilization (11 patients) and a cushingoid appearance (eight patients) the commonest findings. Abnormal biochemical activity was identified in 16 tumours (94 per cent). The primary treatment in 17 patients was surgical. In addition, 12 children, all with carcinomas, had radiotherapy. Adjuvant chemotherapy was given to six patients, three of whom had mitotane (op-DDD). Of those children with a carcinoma 2 are dead, with a median survival of 52 months (range 1–317 months). The three second primary tumours all developed at sites within the field of previous radiotherapy, and proved fatal at 127, 176 and 317 months (median 207 months).
Conclusion: This series confirms the poor prognosis in adreno-cortical carcinoma in childhood, but a complete resection is compatible with cure from the primary disease. The frequency of second, fatal, primary tumours is of particular concern and long-term follow-up is mandatory in survivors, especially if radiotherapy was part of the treatment protocol.

Endocrine/Transplantation 002

Cathecolamine excretion from phaecromocytomas

R. Mihai, N. Wong*, M. Luckett*, E. Sheffield* and J.R.H. Farndon *University Department of Surgery and *Pathology, Bristol Royal Infirmary, Bristol*

Background: The aim of this study was to examine the pattern of cathecolamine secretion in patients with phaechromocytoma and correlate this with the ultrastructural morphology of the secretory granules in tumour cells.
Method: Fifteen patients with adrenal phaeochromocytomas ($n=\ 3$) or paragangliomas ($n=2$) (four men and 11 women, age 17–80 years were studied by measuring urinary-free noradrenaline (NA), adrenaline (Ad) and dopamine (DM). Histopathology examination and immunocytochemistry for specific markers chromogranin, S100, synaptophisin, neurofilament) confirmed the diagnosis. Electron micrographs (× 20000 were obtained from four random fields of each tumour (total surface ≈70 μm^2) and the number and type of secretory granules evaluated by two independent observers blind to the cathecolamine secretory pattern. Large round/elongated medium-density granules characterized adrenaline-type granules (Ad-G), while electron-dense granules lying in a vacuole were of the noradrenaline-type (NA-G).
Results: No correlation was found between NA output and the number/percentage of NA-G, although three tumours with normal NA output had only a minority of NA-G (22 ± 2 per cent). Ad-G were predominant (77 per cent of 173 granules/70 μm^2) in a tumour secreting only Ad but the percentage of Ad-G in six tumours with normal Ad output varied significantly (range 7–89 per cent). It was not possible to evaluate the granule type associated with DM secretion as a tumour secreting excessive amounts DM (14900 nmol/day) and Ad (1570 nmol/day) had a predominance of NA-G (63 per cent of 132 granules/70 μm^2) while in two other DM-secreting tumours (5500 and 4250 nmol/day, respectively) NA-G represented 93 per cent and 13 per cent, respectively. Two adrenal incidentalomas diagnosed as 'non-functional' phaechromocytomas expressed a high number of granules (99 and 172 granules/70 μm^2, respectively) predominantly of Ad type (>90 per cent). There was no significant difference between the number and type of granules evaluated by the two observers (χ^2 test).
Conclusion: Most phaechromocytomas contain a mixture of NA-G and Ad-G and the lack of correlation between cathecolamine secretion and the granularity suggest that other factors are involved in the control of secretion from these tumours.

Endocrine/Transplantation 003

Parathyroidectomy — experience with 170 consecutive cases

M. Menon, P.J. Drew, A. Macdonald, C.M.S. Royston and M.J. Kerin *Hull Royal Infirmary & Castle Hill Hospital, Kingston upon Hull*

Background: The aim of this study was to review the experience with parathyroidectomy performed in Hull over the last 10 years.
Method: A retrospective review of patients' case notes was performed utilizing histological data that had been collected centrally over this period. Presenting symptoms, preoperative investigations, operative findings, histology and biochemical and clinical outcome were reviewed.
Results: One hundred and seventy patients (median age 59 years, range 18–87, male:female, 54:116) underwent 176 parathyroidectomy operations during the study period. Hypercalcaemia was detected incidentally in 131 (77 per cent) asymptomatic patients, 25 (15 per cent) patients initially presented with renal colic, six (3·5 per cent) with psychiatric disturbance, five (3 per cent) with general malaise and three (1·5 per cent) with muscle weakness. Primary hyperparathyroidism was diagnosed in 136 (80 per cent) patients, secondary in 31 (18·5 per cent) and tertiary in three (1·5 per cent). Histology revealed: adenoma in 110, hyperplasia in 40 and carcinoma in one. Of the glands excised 27 were considered to be histologically normal. Six patients underwent re-exploration for persistent hypercalcaemia and five had further parathyroid tissue removed which was found to be normal in three patients, hyperplastic in two and an adenoma in one. One patient suffered a recurrent laryngeal nerve palsy following re-exploration. There were no other major complications in this series.
Conclusion: Primary hyperparathyroidism remains the commonest form of hyperparathyroidism. It is most commonly found incidentally and, in experienced hands, can be effectively and safely treated surgically.

Endocrine/Transplantation 004

Ultrasound-guided unilateral neck exploration compared with bilateral exploration in patients with sporadic primary hyperparathyroidism

B.J. Ammori, M. Madan, T.D. Gopichandran, J.J. Price, M. Whittaker, J.R. Ausobsky and R.M. Antrum *Bradford Royal Infirmary, Bradford*

Background: The aim of this study was to determine the accuracy of ultrasound (US) in preoperative localization of abnormal parathyroid gland(s) in patients with sporadic primary hyperparathyroidism undergoing initial neck exploration, and to compare results of US-guided unilateral neck exploration (UNE) with bilateral exploration (BNE).
Method: Between 1990 and 1995, 72 patients underwent initial neck exploration for primary hyperparathyroidism. There were 26 men and 46 women, with a mean age of 57·4 ± 12·5 years (range 21–80 years). Preoperative US was carried out by an experienced radiologist. Three surgeons adopted a policy of 'selective' US-guided UNE; the fourth surgeon performed routine BNE.

Results: Sixty-three of 72 patients had preoperative US. This was positive in 52 patients; of whom 27 underwent a UNE, 23 had a BNE, and two patients had a UNE converted to a BNE. Patients with 'negative' US ($n = 11$), and those receiving no preoperative localization test ($n = 9$) underwent BNE. The sensitivity, specificity and accuracy of US were 80 per cent (52 of 65), 100 per cent (61 of 61), and 90 per cent (113 of 126), respectively. Both surgical approaches were highly successful, with no significant difference [BNE: 97 per cent (33 of 34) vs US-guided UNE: 93 per cent (27 of 29), $P > 0\cdot05$)]; both incurring very low morbidity.
Conclusion: In the presence of an experienced radiologist US-guided UNE for sporadic primary hyperparathyroidism achieves comparable success rates as for BNE.

Endocrine/Transplantation 005

Starting a new clinical service — is a learning curve a necessity?

K.K. Madhavan, J.L.R. Forsythe and O.J. Garden *Scottish Liver Transplant Unit, Royal Infirmary Edinburgh, Edinburgh*

Background: A learning curve with gradual improvement in results and outcome is considered a necessary experience in the starting of any new clinical service. This study was aimed at testing this hypothesis in the context of the Scottish Liver Transplant Unit which has completed 5 years since inception.
Method: Over the last 5-year period, 163 patients underwent 182 orthotopic liver transplants (OLTs). These patients were studied with both peroperative and postoperative endpoints. Operation time and transfusion requirements as well as 30-day mortality was analysed year by year. Overall patient and graft survival, mortality in fulminant hepatic failure (FHF) transplants, incidence of hepatic artery thrombosis (HAT), primary non-function (PNF) and biliary complications were analysed year by year. Survival data were analysed using the Kaplan–Meir method and significance in survival difference analysed using the log-rank test ($P = < 0\cdot05$).
Results: Over the 5-year period, the overall patient and graft survival was 82 per cent (mean patient survival of 47·8 months) and 75 per cent (mean graft survival of 44 months), respectively. Both operating time and intraoperative blood transfusions showed gradual reduction over the years. The overall 30-day mortality and mortality for FHF transplants showed reduction. The incidence of PNF, HAT and biliary complications remained low through the period.

	1st year	2nd year	3rd year	4th year	5th year
Transplants	31	34	45	44	34
30-day deaths	5	3	6	4	1
% mortality	16	9	13	9	3
FHF deaths	1 (3)*	3 (5)*	1 (7)*	0 (7)*	0 (5)*
HATs**	1	0	1	1	0

*The values in brackets indicate the total number of OLTs for FHF for the year; **Only acute episodes during index admission are included.

Conclusion: Although a learning curve is not a must for a new clinical service and results can be good from the start, experience results in further improvement in various factors which may have an impact on overall results.

Endocrine/Transplantation 006

The role of nitric oxide in renal ischaemia reperfusion injury

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Background: This study investigated the role of nitric oxide (NO) in renal warm ischaemia reperfusion (WI/R) injury.
Method: Groups of rats underwent bilateral renal WI/R (15–45 min/20 or 80 min) prior to a left nephrectomy for analysis of renal NO (nitrate nitrite) and oxidative DNA damage (8-oxodG). The glomerular filtration rate (GFR) was measured (days 2 and 7) prior to killing for right kidney analysis and morphology. A further group received the NO synthase (NOS) inhibitor L-NAME (50 mg/kg intravenously) before WI.
Results: Following WI renal NO rose early and was maintained to day 7 whilst 8-oxodG peaked at 20 min. The decrease in the GFR was in line with the WI duration as was the morphological damage L-NAME reduced NO to day 7 with a simultaneous decrease in 8-oxodG at 20 mm but elevation at day 7. A deterioration in GFR but not morphology was evident.

	Nitric oxide (μM) reperfusion time		
WI group	20 min	80 min	Day 7
Control		442 (17)	426 (22)
15 min	762 (95)‡	865 (57)†	1110 (48)†
30 min	862 (44)†	1010 (142)†	1130 (60)†
45 min	997 (49)†	982 (54)†	1080 (29)†
L-NAME	562 (69)†		867 (75)‡

Results are mean (SEM); *$P \leq 0\cdot05$ vs control; †$P \leq 0\cdot01$ vs control; ‡$P \leq 0\cdot01$ vs control. The control for group L-NAME is WI group 45 min.

	8-oxodG (/10^5dG) reperfusion time			GFR (ml/min) reperfusion time	
WI group	20 min	80 min	Day 7	Day 2	Day 7
Control		2·0 (0·7)		2·5 (0·1)	2·5 (0·2)
15 min	6·7 (1·0)*	1·8 (0·5)	0·1 (0·01)	1·3 (0·2)	1·7 (0·2)
30 min	5·2 (1·7)*	2·6 (0·9)	4·1 (0·5)	0·8 (0·1)‡	1·4 (0·1)
45 min	14·6 (0·9)‡	3·5 (0·5)	2·0 (0·5)	0·6 (0·1)‡	1·2 (0·1)*
L-NAME	4·5 (0·8)†		2·9 (0·01)‡	0·3 (0·1)*	0·6 (0·1)‡

Results are mean (SEM); *$P \leq 0\cdot05$ vs control; †$P \leq 0\cdot01$ vs control; ‡$P \leq 0\cdot01$ vs control. The control for group L-NAME is WI group 45 min.

Conclusion: In recoverable renal WI/R injury NO increased early and remained elevated through to day 7. NOS inhibition ameliorated early renal damage but exacerbated the late injury suggesting the early burst of NO is cytotoxic but overall NO may exert a protective effect.

Endocrine/Transplantation 007

Kidney damage at organ retrieval — the facts

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Background: This study aimed to determine the incidence, risk factors and outcome of kidney damage sustained at organ retrieval.
Method: Data were obtained from the UK Transplant Support Service Authority on all kidneys retrieved from cadaveric donors within the UK and Republic of Ireland, between January 1992 and December 1996. The incidence of damage reported at retrieval and at transplantation was recorded. In addition the outcome of the kidneys, whether used locally, exported or discarded was determined. Age of donor, the type of retrieval and the number and type of operating surgical teams involved were all recorded. Statistical analysis used Cox regression models fitted to renal allograft survival data.
Results: A total of 9014 kidneys were retrieved from cadaveric donors. Of these, 1726 (19 per cent) were reported as damaged, but only 78 were not transplanted because of the recorded retrieval injury. Of the transplanted kidneys, only 16·5 per cent were reported as damaged by both the donor and recipient centres. In multiorgan retrievals where the liver surgeon retrieved both liver and kidneys, the recorded renal injury rate was 16·8 per cent. Where liver and kidney teams were present at retrieval the injury rate was 21·2 per cent, compared with 26 per cent at kidney only retrievals. Kidneys retrieved and transplanted locally had a 14 per

cent incidence of injury, whereas those exported and transplanted elsewhere had a 30 per cent injury rate. The range of donor age was 0 to 76 years. Sixty-two per cent of damaged kidneys came from donors greater than 40 years of age. Donor age had a significant effect on both 1- and 3-year graft survival ($P = 0{\cdot}0001$) whereas kidney damage alone did not significantly affect 1- ($P = 0{\cdot}2$) or 3-year survival ($P = 0{\cdot}066$).

Conclusion: Kidney damage is both common, under-reported and more likely to occur in the elderly donor where only kidneys are retrieved by a renal team. Although this may reflect poorer surgical exposure or relative inexperience of the operating surgeon, damaged but transplantable kidneys tend to be exported and graft survival is not significantly affected.

Endocrine/Transplantation 008

Piggyback vs classical orthotopic liver transplantation, a retrospective analysis

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Background: Piggyback orthotopic liver transplantation (PBOLT) has potential advantages over the classical technique (COLT), because it avoids the need for veno-venous bypass. The aim of this study was to compare these two surgical techniques in terms of transfusional requirements, morbidity and mortality.

Method: The results of a consecutive series of 66 PBOLT were compared with a previous cohort of 43 COLT. Data were obtained retrospectively from standard proforma. The indications for the PBOLT were chronic liver failure in 54, fulminant hepatic failure in six and six re-transplants. Although a temporary portocaval shunt was fashioned in 34 patients none required veno-venous bypass. Of the 43 COLT, 29 were for chronic liver failure, five for fulminant hepatic failure and nine re-transplants. All 43 utilized veno-venous bypass.

Results:

	Blood product transfused		
	Red blood cells	Fresh frozen plasma	Platelet
Piggyback ($n = 66$)	6·4 units	3·9 units	6·4 units
Classical ($n = 43$)	10·5 units	9·9 units	7·2 units

	Complications				
	Renal failure	Haemorrhage	Hepatic artery thrombosis	Venous outflow obstruction	30-day mortality
Piggyback	17 (25%)	3	4	2 (acute) 4 (chronic)	5
Classical	9 (21%)	3	3	0	3

Conclusion: Although the piggyback technique avoids the specific complications related to veno-venous bypass and has a reduction in the transfusional requirements, graft outflow obstruction remains a potential source of morbidity. A prospective randomized trial is required to determine the optimum surgical technique for adult OLT.

Endocrine/Transplantation 009

The spleen as a site for human islet autotransplantation

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Background: The spleen can be used as an alternative site to the liver for human islet autotransplantation (AT). Islets have been infused via the short gastric (SG) veins in an attempt to avoid splenic vein thrombosis and in cases where the splenic vein cannot be preserved during the pancreatectomy procedure. The aim of this study was to assess the anatomical variation of the SG veins.

Method: A total of 27 human cadavers were studied (12 male, 15 female) in order to assess splenic venous drainage.

Results: A total of 76 SG veins were identified. The median number was three (range 1 to 6). In over 80 per cent of cases there was a direct communication between the short gastric veins and the other draining veins of the spleen (i.e. splenic vein or left gastroepiploic [LGE] veins). Only SG vein 1 (80 per cent), 2 (26 per cent) and 3 (9 per cent) communicated directly into the splenic pulp the remainder communicating with the splenic vein (85 per cent) or the LGE (15 per cent).

Conclusion: This study suggests that during splenic islet AT via the SG veins there is great potential for reflux into the portal venous system. This could have dramatic consequences upon portal pressure and portal hypertension following a combined intra-portal and splenic islet AT due to reflux of 'splenic' islet tissue back into the portal vein.

UGI 001

Laparoscopic Nissen vs anterior fundoplication: a randomized trial

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Background: The aim of this study was to determine whether a laparoscopic anterior fundoplication is associated with a lower incidence of postoperative dysphagia than laparoscopic Nissen fundoplication, whilst still achieving a durable antireflux barrier. Initial outcomes are presented.
Method: One hundred and seven patients presenting for laparoscopic antireflux surgery were prospectively randomized to undergo either a Nissen fundoplication (53) or an anterior 180° hemifundoplication (54). Patients were blinded to which procedure had been performed. Clinical assessment was performed by a blinded independent investigator, who used multiple standardized clinical grading systems to assess the dysphagia, heartburn and patient satisfaction 1, 3 and 6 months following surgery. Objective measurement of lower oesophageal sphincter pressure, oesophageal emptying time, distal oesophageal acid exposure and endoscopic healing of oesophagitis was performed.
Results: Operating time was similar for the two procedures. Whilst resting and residual lower oesophageal sphincter pressures were lower (30 vs 17 and 15 vs 5) following anterior fundoplication, oesophageal emptying times (59 vs 54 s), acid exposure times and ability to heal oesophagitis were similar. At 3 months follow-up the clinical outcomes of postoperative dysphagia, relief of heartburn, and overall satisfaction were similar for the two procedures. At 6 months patients who had undergone an anterior fundoplication experienced less dysphagia and were more satisfied with their clinical outcome.
Conclusion: Laparoscopic anterior fundoplication achieved equivalent control of reflux and more physiological postoperative manometry parameters. It did not result in improvement in the measured clinical outcomes at 3 months but at 6 months there was less dysphagia.

UGI 002

The potential dangers of laparoscopic repair of perforated peptic ulcers

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Background: The gains that accompany elective upper gastrointestinal laparoscopic surgery are particularly obvious. There is a tendency to assume this will apply to those with generalized peritonitis due to perforated peptic ulcers.
Method: This non-randomised concurrent cohort study compared 15 consecutive laparoscopic repairs of perforated peptic ulcers (Lap group) with a concurrent group of 15 consecutive open repairs (Open group).
Results: There were no differences preoperatively in age ($P=0{\cdot}32$), sex ($P=0{\cdot}31$), duration of perforation ($P=0{\cdot}73$), APACHE II score ($P=0{\cdot}27$), ASA grade ($P=0{\cdot}31$), or hourly urine output ($P=0{\cdot}09$) between the two groups. The mean duration of laparoscopic surgery was 77 min compared with 72 min with open repair ($P=0{\cdot}54$). One patient had a prepyloric ulcer, the rest were anterior or superior duodenal ulcers. A median of two sutures were used (range 2–4) to secure the omental patch. Laparoscopic lavage used a mean of 5·5 L compared with 4·0 L ($P=0{\cdot}03$), there were three conversions. ITU care was required in three patients in the Lap group (two with renal failure) and two patients in the Open group (no renal failure). One patient in each group died. Postoperatively the duration of nasogastric drainage, intravenous fluid administration and time to oral fluids and diet showed no differences in gastrointestinal tract recovery. The median duration of stay of 6 days in the Lap group did not differ from the 7 days in the Open group.
Conclusion: This comparison provides anecdotal evidence that the pathophysiological insult of laparoscopy in the setting of generalized peritonitis might increase the perioperative risk of organ failure particularly renal and provides a mandate for a prospective randomized controlled trial.

UGI 003

Scanning laser doppler flowmetry and intra-luminal recirculating gas tonometry in the assessment of gastric perfusion during oesophageal resection

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Background: Of the aetiological factors associated with leak and benign stricturing of the anastomosis following oesophageal resection and reconstitution of gastrointestinal continuity with a gastric tube, ischaemia caused by poor perfusion at the gastric end of the anastomosis is thought to be important. Scanning laser Doppler flowmetry (which creates a perfusion image) and continuously recirculating gas tonometry are new techniques that can assess changes in tissue perfusion and in this study, their ability to detect changes in gastric perfusion during oesophageal resection and formation of gastric tubes was assessed.
Method: Sixteen patients undergoing oesophageal resection for malignancy were studied. Tonometer balloons were placed in the stomach and proximal jejunum (alongside a feeding jejunostomy feeding catheter). Measurements of gastric and jejunal intra-mucosal pHi and a laser Doppler scan of the stomach were made at three time points: prior to gastric mobilization, after division of left gastric, short gastric and left gastroepiploic vessels and finally after formation of the gastric tube. In each subject, from a grey-scale photographic image of the stomach produced by the scanning laser, identical regions of interest (ROIs) each of $1{\cdot}5\,\text{cm}^2$ were interrogated from each scan, these representing the area of anastomosis, the gastric corpus and the antrum. Mean perfusion units (PUs) from the 1750 individual measurements taken within the ROI were then calculated for each of these areas. Mean measurements for the whole stomach or gastric tube were also made.
Results: There were significant falls in perfusion measured with the scanning laser Doppler in all the subjects between each time point and in all areas of the stomach. Mean perfusion of the stomach was 530 PUs prior to mobilization and this fell to 313 PUs after mobilization representing a mean fall of 40 per cent. There was a gradient of reduced perfusion between the antrum (fall 25 per cent, $P<0{\cdot}05$) and the area used for the anastomosis in the fundus (mean fall 56 per cent, $P<0{\cdot}001$). After formation of the gastric tube, mean perfusion at the anastomosis site fell to a mean of 197 PUs (mean fall 61 per cent, $P<0{\cdot}0005$). Prior to mobilization mean gastric and jejunal pHi were 7·37 and 7·46, respectively. These figures changed to 7·18 and 7·36, respectively after mobilization and to 7·29 and 7·38 after anastomosis formation.
Conclusion: This study confirms our pilot study that both these techniques can be used intra-operatively to assess changes in gastric perfusion during oesophagectomy and we have observed significant falls in perfusion in that area of the stomach used for the gastro-oesophageal anastomosis between the start and end of surgery. Further study is needed to assess if these methods can be used to predict ischaemia-related anastomotic complications.

UGI 004

Efficacy and incidence of post-fundoplication symptoms at a median of 5 years following open Watson fundoplication

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Background: While ease of performance laparoscopically has encouraged dissemination of the Watson partial wrap fundoplication, independent assessment of its claims to provide effective relief of reflux symptoms with a lower incidence of super-competence type symptoms remains lacking. The aim of this study was to establish the long-term efficacy and incidence of post-fundoplication symptoms from an independent experience with the open Watson fundoplication.
Method: Data from 49 patients having undergone an open Watson fundoplication over an 8-year period were reviewed and patients were interviewed to establish their current DeMeester Symptom Score for reflux and the incidence of post-fundoplication symptoms. A Visick grading was determined separately in each case. The Paired Wilcoxon Rank Sum Test was used for statistical comparisons.
Results: Oesophagitis was noted endoscopically in 67 per cent with 92 per cent having DeMeester symptom scores of ≥4. Pre-operative 24-h pH studies (performed in 85 per cent of cases) documented a median of 12·5 per cent time spent at pH <4 when supine, a median of 14 reflux episodes >5 min and a median composite DeMeester score of 85. Post-operative studies (in 53 per cent of cases) yielded equivalent values of 0, 1 and 14 respectively (all $P<0{\cdot}01$). Follow-up interviews were completed in 42 (86 per cent) at a median interval of 5 years (range 1–9 years). The DeMeester symptom score was 1 or less in 86 per cent ($P<0{\cdot}001$). On direct questioning failure of eructation was noted in one (2·4 per cent) and inability to vomit in six (14·3 per cent). No symptoms at all were elicited in 66·7 per cent (Visick I), mild symptoms in only 26·1 per cent (Visick II), while 4·8 per cent required treatment but were controlled (Visick III) and 2·4 per cent were not fully controlled.
Conclusion: These data suggest that the Watson fundoplication gives satisfactory control of reflux with a low incidence of post-fundoplication symptoms and a very high rate of overall patient satisfaction in the medium to long term. Similar results may be anticipated in laparoscopic Watson fundoplication.

UGI 005

Oesophago-gastric junction cancer is related to alcohol consumption but not smoking

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Background: The aim of this study was to identify any association between tobacco and/or alcohol consumption and cancers involving the oesophago-gastric junction, compared with those confined either to the oesophagus or stomach. Any association with subsite was defined by comparing age at diagnosis in those who consume tobacco/alcohol with those that did not.
Method: Fourteen hundred cases of cancer of the oesophagus or stomach in 1993 were identified from the North Western Regional Cancer Registry (population 4,030,800). Case-note review identified 1067 new diagnoses of oesophageal or gastric cancer. Tumour site was recorded as involving the oesophago-gastric junction, or oesophagus/stomach alone. Consumption of cigarettes and alcohol were recorded from the notes. Smokers were compared with non-smokers. Those consuming more than 5 units of alcohol per week were compared with those who did not.
Results: Three hundred and thirty-two cancers involved the oesophago-gastric junction, 281 were confined to the oesophagus, and 454 to the stomach. Three hundred and sixty-one (54·1 per cent) men and 120 (27·3 per cent) women had smoked. Smokers of both sexes developed carcinoma of the oesophagus and stomach at a significantly younger age than non-smokers, whereas there was no such difference for cancers of the oesophago-gastric junction. One hundred and twenty-nine (19·3 per cent) men and 14 (3·2 per cent) women consumed more than 5 units of alcohol per week. Consumption of more than 5 units of alcohol per week was associated with significantly younger age at diagnosis in men for cancers at all sites.

	Oesophagus		Oesophago-gastric junction		Stomach	
Median age (years)	Male	Female	Male	Female	Male	Female
Non-smokers/drinkers	71·2	76·6	68·1	72·4	75·5	77·6
Smokers	64·9**	68·5**	66·6	67·7	69·6**	69·2**
>5 units/week	59·8**	—	63·3*	—	68·0*	—

*$P<0{\cdot}05$; **$P<0{\cdot}01$.

Conclusion: Cancer involving the oesophago-gastric junction represents an epidemiologically distinct disease entity, associated with male sex and younger age at diagnosis compared with cancers confined to the oesophagus and stomach. Oesophago-gastric junction cancer and alocohol consumption are associated with different age at diagnosis, whereas smoking is not, unlike cancer confined to the oesophagus or stomach.

UGI 006

Peritoneal fluid cytology in the staging of oesophageal and gastric malignancies

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Background: The aim of this study was to examine the role of peritoneal fluid cytology in laparoscopic staging of oesophageal and gastric malignancies.
Method: Data were audited prospectively for 125 patients with gastro-oesophageal malignancy who were assessed and staged in a specialist unit. Laparoscopy was carried out in 71 (57 per cent) patients (26 oesophageal and 45 gastric; median age 67 years). Saline instilled into the peritoneal cavity was aspirated and sent for cytology. Ascites, if present, was sampled separately. Fluid for cytology was obtained in 56 (79 per cent) patients.
Results: Early (TNM stage I and II) disease was present in 13 (18 per cent) of the patients who were staged with laparoscopy. Stage III disease was present in 28 (39 per cent) of the patients while the remaining 30 (42 per cent) had advanced stage IV disease. After staging curative or palliative resection of the tumour was carried out in 47 (66 per cent) of the patients. Peritoneal fluid aspirate was positive for malignant cells in 11 (19·6 per cent) and negative for 45 (80·4 per cent). There were no cases of positive cytology in stage I and stage II disease. Positive results were obtained in two (9 per cent) of the 22 patients with stage III disease and in nine (36 per cent) of the 25 patients with stage IV disease. There was a significant correlation between positive cytology and stage IV disease (χ^2 $P=0{\cdot}0007$). Median survival for stage III and stage IV disease was 31·3 months and 5·1 months, respectively (log rank $P<0{\cdot}00001$).
Conclusion: While positive peritoneal cytology is indicative of advanced disease, in 64 per cent of the patients with stage IV disease the peritoneal aspirate did not yield any malignant cells. Routine peritoneal fluid cytology does not offer any significant contribution to the staging of gastro-oesophageal cancers.

UGI 007

An audit of treatment of cancer of the oesophagus in a district general hospital

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Background: The aim of this study was to audit the treatment of cancer of the oesophagus in a District General Hospital, and to compare results with regional and national audit studies.
Method: The treatment of 132 proven cases of cancer of the oesophagus seen between January 1990 and October 1997 was reviewed. All patients were under the care of the same Consultant surgeon (ARQ). Patients were identified from the computerized patient administration system, which was cross-checked with pathology records and operating theatre registers. The results were compared with those in a series from Leeds and a national audit study.
Results: Of 132 patients, 86 were male and 46 were female. The lesion was in the upper oesophagus in seven, middle in 30 and lower in 95 patients. Histology, available in 131/132 cases revealed adenocarcinoma in 84 squamous cell carcinoma in 44 and other neoplasms in three. Metastases at diagnosis were identified in 24/132 patients. Surgery was performed in 52/132 patients — resectional procedures in 37 (17 Ivor Lewis, 11 cardio-oesophagectomies, seven transhiatal oesophagectomies in two three-stage procedures) and palliative surgical intubation in 15. Therapeutic endoscopic procedures were performed in 50 patients — dilatation in 21, Atkinson tube insertion in 22, laser therapy in two and wall stent insertion in five. Radiotherapy was given to 37 patients — curative in eight and palliative in 29. Fourteen patients received a combination of two or more treatment modalities. The complication rate among surgically treated patients was 40 per cent and the 30-day hospital mortality rate was 11·5 per cent compared to 14 per cent in a survey of 50 UK specialist thoracic centres. The median survival for all patients was 6 months — broken down as 9 months for surgically treated cases, 6 months in endoscopically treated cases and 6 months for those receiving radiotherapy.
Conclusion: This series has demonstrated a preponderance of male patients, and those with adenocarcinoma of the lower oesophagus, the latter finding mirroring recent trends in the West. Morbidity and mortality figures in Macclesfield compare favourably with those seen in regional and national audit studies.

UGI 008

The pattern of recurrence of adenocarcinoma of the oesophago-gastric junction

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Background: Previous reports have suggested that 80 per cent of gastric cancer recurrences are with peritoneal disease. The aim of this study is to examine whether tumours of the oesophago-gastric junction conform to this pattern of recurrence or exhibit a distinct natural history.
Method: The follow-up of patients with adenocarcinoma of the lower oesophagus and gastric cardia who had undergone surgery with curative intent since 1991 was examined for evidence of recurrent malignant disease. Clinical evaluation was supported by ultrasound, computerized tomography, radio-isotope bone scan, endoscopy and laparotomy each with biopsy and histology where appropriate. Patients in whom the diagnosis of recurrent disease was unsupported other than by clinical impression were excluded. Statistical analysis was by the χ^2-squared and Mann–Whitney U-tests.
Results: One hundred and twenty-two patients with oesophago-gastric junction tumours (53 gastric cardia (IGCA* Type 2)) and 69 adenocarcinomas of the lower oesophagus (IGCA Type 1) have been followed up for a median of 19 (1–84) months. There was a similar sex and age distribution for Type 1 and Type 2 junctional adenocarcinomas (male:female 3·4:1 vs 6·6:1; age 63 (40–77) vs 70 (42–78). Forty-one patients developed proven recurrent disease. The median time to recurrence was 7 (1–28) months and was similar between Types 1 and 2 subgroups. The median time to death thereafter was 2 (1–15) months. Only three cases of peritoneal dissemination were found among the 17 Type 2 junctional cancer recurrences and only 1/24 among the Type 1 group. The most frequent mode of dissemination for both groups was haematogenous spread (14/24 of Type 1 and 10/17 of Type 2 recurrences). Haematogenous dissemination accounted for a significantly greater proportion especially of first-year failures (12/15 vs 11/26; $P<0{\cdot}05$). The most frequent sites of haematogenous spread were to liver (9), bone (10), brain (3) and lung (3). Local lymph node recurrence occurred in 6/24 cases of Type 1 and 4/17 Type 2 tumour recurrences, most frequently to coeliac or porta hepatic nodes (7/10). Local recurrence occurred in 7/24 and 8/17 cases, respectively. Disease-free survival correlated inversely with lymphatic ($P<0{\cdot}001$), and neural ($P=0{\cdot}002$) invasion and lymph node positivity ($P<0{\cdot}001$).
Conclusion: The natural history of cardial tumour recurrence is similar to that of adenocarcinoma of the lower oesophagus and differs from more distal gastric cancers. Recurrence of these oesophago-gastric junction tumours is by haematogenous and lymphatic rather than transcoelomic spread. This finding has implications for the choice of route of administration of adjuvant therapy for junctional compared with other gastric tumours.

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*International Gastric Cancer Association classification.

UGI 009

Clinical and endoscopic response to neoadjuvant therapy for carcinoma of the oesophagus

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Background: Recent evidence indicates that neoadjuvant therapy confers a survival advantage to patients with oesophageal cancer. Local tumour response to neoadjuvant therapy was evaluated by clinical, endoluminal ultrasound (EUS) and histopathological criteria in patients with carcinoma of the oesophagus.
Method: Sixteen patients with oesophageal cancer, adenocarcinoma ($n=11$), squamous carcinoma ($n=5$) were studied prospectively. Patients underwent clinical assessment and EUS pre- and post-neoadjuvant therapy. Dysphagia was scored on a scale of 1 to 4. Twelve patients received radiotherapy (40 Gy) and two cycles of cisplatin/5-FU, whilst four patients with distal tumour extension received four cycles of epirubicin, cisplatin and 5-FU. Twelve patients underwent oesophagectomy on completion of neoadjuvant therapy.
Results: Tumour depth determined by EUS was significantly reduced following treatment. EUS did not demonstrate a reduction in T-stage for any patient, while three patients were down-staged from N1 to N0. The effects of treatment are summarized in the tables below.

EUS findings	Before	After
Depth (mm)	12·4 ± 1·7	9·1 ± 0·9*
Length (cm)	6·2 ± 1·1	4·9 ± 0·8

*$P<0{\cdot}05$ paired *t*-test.

Response	Adenocarcinoma	Squamous carcinoma
↓ Dysphagia score	2/11 (18%)	4/5 (80%)*
Tumour depth before/after	1·0 (IQR 0·8–1·4)	2·5 (1·1–3·6)**
100% pathological response	0/7 (0%)	3/5 (60%)*

*$P<0{\cdot}05$ Fisher's exact test, **$P<0{\cdot}05$ Mann–Whitney U-test.

Two patients with adenocarcinoma had progression of nodal disease during therapy.
Conclusion: EUS did not detect tumour regression according to T-stage, possibly due to an inability to differentiate tumour from post-treatment fibrosis, rather, serial EUS assessment of tumour depth may prove to be useful in determining the response to therapy. Based on clinical assessment, EUS and histopathology, patients with oesophageal squamous carcinoma responded favourably to neoadjuvant therapy, while such a response was infrequent in patients with adenocarcinoma.

H & P 001

Audit of surgical management of liver trauma: a single-unit experience

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Background: The aim of this study was to provide a retrospective audit of the surgical management of patients with liver trauma.
Method: We studied 46 consecutive patients (36 male, 10 female) with a median age of 43 years (range 21–67) who were transferred to our Department after sustaining a blunt abdominal trauma ($n=44$) or a penetrating injury ($n=2$) between 1994 and 1996. On admission, all patients were haemodynamically unstable. After successful resuscitation a diagnosis of intra-abdominal bleeding was made using peritoneal lavage. Subsequently, emergency laparotomy revealed liver trauma in all cases classified according to the Liver Injury Scale (Grades I–V).
Results: Grade I ($n=17$), II ($n=16$), III ($n=11$) and V ($n=2$), respectively. Associated injuries included splenic rupture ($n=15$), gallbladder avulsion ($n=5$), inferior vena cava laceration ($n=3$), shattered kidney ($n=4$) and miscellaneous ($n=17$). Various procedures were carried out for control of liver bleeding as follows: topical haemostasis ($n=17$), hepatorrhaphy by the finger fracture technique plus omentoplasty ($n=3$), deep liver suturing with omentoplasty ($n=22$) and resectional debridement ($n=4$). Splenectomy ($n=15$), cholecystectomy ($n=4$), nephrectomy ($n=4$), small bowel resection ($n=1$) and suture of various lacerations ($n=5$) were also performed at the same time. Complications developed in 10 (21·7 per cent) patients whilst the overall mortality was 8·7 per cent (four patients).
Conclusion: Proper and experienced management of liver trauma in a well-organized trauma centre results in a reasonable complication rate with acceptable mortality.

H & P 002

How and where should blunt liver trauma be managed?

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Background: There has been an increasing trend for non-operative management of liver trauma. We report 34 tertiary referral cases of severe liver injury transferred to the Liver Unit in the last 6 years.
Method: Thirty-four patients with blunt trauma were treated, of which 12 (35 per cent) were managed conservatively. Twelve of the 15 patients who had undergone surgery elsewhere required reoperation and a further seven underwent initial surgery in the Liver Unit. Nine major hepatic resections were performed, the remainder either had liver packs removal or haemostatic suturing.
Results: The overall mortality was eight patients (25 per cent), of which five had major anatomical resections, the other three liver packing alone. Four of the patients who died had other intra-abdominal injuries, two pancreatic and two splenic. The mean hospital stay for the operative group was 20 days. All patients treated conservatively made a good recovery, mean hospital stay was 12 days.
Conclusion: Conservative management of major blunt liver trauma is a safe and justified treatment modality, provided that the initial assessment of the patient is done appropriately. Treatment must be performed in specialized units where extensive surgical procedures can be offered. We recommend that patients with blunt abdominal trauma admitted to district general hospitals undergo contrast enhanced computed tomography (CT) scan prior to surgical treatment, several patients had delayed surgery at the admitting hospital without CT imaging — had this been done we believe these patients would have been referred immediately without initial exploration.

H & P 003

Phase I study of early nasogastric feeding in severe acute pancreatitis

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Background: Recent work has suggested that enteral feeding may reduce the inflammatory response in severe acute pancreatitis, however, the placement of nasojejunal tubes in such patients carries risk from the need to transfer critically ill patients for X-ray screening or fibreoptic endoscopy. We undertook a Phase I study to assess the safety of nasogastric feeding in patients with severe acute pancreatitis.
Method: Twenty-six consecutive patients admitted to our unit with severe acute pancreatitis received feeding via nasogastric tube within 48 h of arrival. Severity of disease was defined by Glasgow Prognostic Criteria, APACHE II Score, C-reactive protein and contrast-enhanced computed tomography scan. All patients received full supportive care with cardioventilatory and renal support as required.
Results: Aetiology was identified as cholelithiasis (18 patients); ethanol (five) and miscellaneous (three). Median Glasgow Score was 5 (range 2–7); APACHE II Score 10 (4–28) and C-reactive protein 240 mg/L (79–385). Sixteen patients had significant pancreatic and peripancreatic necrosis. Eighteen patients underwent ERCP, six necrosectomy for infected necrosis or failure to improve and four internal drainage of pseudocyst. Eleven patients required ventilatory support, six of whom also required inotropic support with three also having renal dialysis. There were two deaths. The feed was well-tolerated in all but four patients. There was no evidence of recurrence of abdominal pain nor a secondary rise in C-reactive protein concentration on commencement of feeding.
Conclusion: We conclude that early nasogastric feeding in severe acute pancreatitis appears to be safe, well tolerated and worthy of further study.

H & P 004

A policy of urgent laparoscopic cholecystectomy for acute gallstone-related symptoms

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Background: Although the merits of urgent cholecystectomy for acute gallstone-related symptoms have been debated for decades, in the UK, particularly in the laparoscopic era, logistics have limited its assessment.
Methods: This study prospectively evaluated a policy of urgent laparoscopic cholecystectomy in all patients admitted as emergencies ($n=51$) over a 9-month period to a single surgical unit with acute cholecystitis (22), empyema of the gallbladder (8), biliary colic (15), pancreatitis (three) or jaundice (three). The results were audited and compared with those referred electively ($n=88$).
Results: There were no preoperative differences between the acute and elective groups in age (mean 51·6 vs 53·1, $P=0{\cdot}66$), sex (31 female vs 63, $P=0{\cdot}19$), body mass index (mean 27·8 vs 29·8, $P=0{\cdot}076$) or ASA grade >2 (11 vs 9, $P=0{\cdot}066$). Preoperative ultrasonography ($P=0{\cdot}0001$)

and liver function tests ($P=0{\cdot}0002$) were significantly different. Surgery in the acute group took significantly longer (mean 79 vs 64 min, $P=0{\cdot}0022$), involved more modifications in surgical technique ($P=0{\cdot}0007$) and accounted for all three conversions ($P=0{\cdot}021$) suggesting an increased difficulty. There were no deaths or reoperations. One cystic duct leak occurred requiring endoscopic stenting. Median hospital stay in the acute group was 4 days and in the elective group 2 days ($P<0{\cdot}0001$). Postoperative stay was also longer (median of two nights compared with 1 night, $P=0{\cdot}0004$).
Conclusion: The results suggest that a policy of urgent laparoscopic cholecystectomy by experienced surgeons in all patients admitted with acute symptoms can be carried out safely with minimal morbidity and economic and social advantages which make it the management of choice.

H & P 005

Magnetic resonance cholangiography reduces the need for ERCP prior to laparoscopic cholecystectomy

S. Dwerryhouse, E. Brown* and M. Vipond *Departments of Surgery and *Radiology, Gloucestershire Royal Hospital, Gloucester*

Background: With the advent of laparoscopic cholecystectomy many surgeons have adopted a policy of selective pre-operative endoscopic retrograde cholangiopancreatography (ERCP) for patients with risk factors for common bile duct (CBD) stones. As ERCP is invasive with a well documented morbidity we have evaluated magnetic resonance cholangiography (MRC) to detect CBD stones prior to laparoscopic cholecystectomy.
Method: All patients scheduled for operation for symptomatic gallstones underwent MRC if they had one or more risk factors for CBD stones: dilated CBD >7 mm on ultrasound, previous documented jaundice or pancreatitis, previous or current abnormal liver function tests. Patients then underwent ERCP within 1 week; if ERCP failed peroperative cholangiography was performed.
Results: Over a 20-month period, 37 patients were studied. Two patients failed to complete MRC because of claustrophobia. ERCP was unsuccessful in four patients. MRC identified six of seven patients found to have CBD stones. Two patients were incorrectly diagnosed with CBD stones by MRC. In this study MRC had a sensitivity of 86 per cent, specificity of 93 per cent, positive predictive value of 75 per cent and negative predictive value of 96 per cent.
Conclusion: MRC is a simple non-invasive method for pre-operative screening for CBD stones. In this study it would have reduced the need for ERCP by three-quarters.

H & P 006

Management of intrahepatic stone disease with a subparietal hepaticojejunal access loop

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Background: Intrahepatic stone disease (IHSD) presents difficulties in management because of recurrent stone and stricture formation and the difficulty of stone removal from within the intrahepatic ducts. We report our experience with the management of this condition after surgical removal of stones and formation of a subparietal hepaticojejunal access loop to allow postoperative percutaneous radiological access for stone removal and stricture dilatation.
Method: Between 1985 and 1997, 21 patients, mean age 34 years (range 24–66 years); 10 male and 11 female with IHSD have undergone surgery and formation of a hepaticojejunal access loop. Patients were followed prospectively and details of the number and type of procedures performed, stone clearance rates, morbidity and subsequent outcome were recorded.
Results: The distribution of stones within the liver was predominantly left-sided. Left lobe was the site of disease in 67 per cent (14/21) the right lobe in one (5 per cent) and bilateral disease in 28 per cent (6/21). There was associated atrophy of the left lobe in six patients who underwent additional left lateral segmentectomy at the initial operation. Following surgery, access loops were used for stone removal or stricture dilatation 97 times, median of four (range 0–25) procedures per patient. Complete stone clearance was achieved in 86 per cent (18/21) of patients with partial clearance in the remaining three. Stones were removed and crushed using a basket, snare or balloon and strictures dilated with a balloon. Access via the loop failed on only two occasions. Patients received parenteral antibiotics for 24 h after the procedure. There were no major complications and no mortality associated with the procedures.
Conclusion: The sub-parietal access loop permits long-term access to the biliary system allowing removal of stones and dilatation of strictures in IHSD with low morbidity.

H & P 007

Lessons learnt from day-case laparoscopic cholecystectomy

J.A. Grabham, A. Knight, D. Raitt and W.W. Barrie *Leicester General Hospital, Leicester*

Background: Day-case laparoscopic cholecystectomy has failed to become popular in the UK due to concerns about safety and patient tolerance. We have audited our early experience of the procedure in an attempt to identify and address any problems.
Method: A case-note review was performed of all patients who underwent attempted day-case laparoscopic cholecystectomy between January 1995 and May 1997, supplemented by a postal questionnaire.
Results: During the 28-month period, 50 patients underwent attempted day-case laparoscopic cholecystectomy. Their mean age was 50 years (range 21–57 years) and 46 were female. All were either ASA I or II. The mean operating time was 80 min (range 40–190 min). Sixteen patients (32 per cent) required overnight admission. The most common reasons for admission were postoperative nausea and vomiting (nine patients) and abdominal pain (five patients). One patient was readmitted 4 days after surgery with jaundice from a retained stone in the common bile duct and was successfully treated by endoscopic sphincterotomy. Two patients developed umbilical wound infections which settled on oral antibiotics. Sixty per cent of patients responded to the questionnaire. Of those who had been successfully treated as day-cases, 18 per cent described significant postoperative nausea and vomiting with 82 per cent experiencing significant abdominal pain during the first 24 h after discharge. The majority (82 per cent) were happy to have been managed as day-cases but three would have preferred overnight admission.
Conclusion: Day-case laparoscopic cholecystectomy can be safely performed in a British day surgery unit but approximately one third of patients may require overnight admission, largely due to nausea and abdominal pain. These symptoms are also common after successful same-day discharge and additional measures must be taken to address these problems.

H & P 008

The need for a pre-operative ERCP predicts difficult laparoscopic cholecystectomy

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Background: Minimal access surgery and ERCP have made invaluable contributions to the management of patients with biliary stone disease.

The aim of this study was to confirm a clinical suspicion that the need for preoperative ERCP would predict difficult laparoscopic cholecystectomy (LC).

Method: A consecutive series of 70 patients who had an ERCP and a subsequent LC between December 1992 and December 1996 were analysed. The variables studied included conversion rates, operative time, operative difficulty, duration of hospital stay, analgesic requirement and complications. An age- and sex-matched control group of 134 patients who had LC without preoperative ERCP were identified. This group were also matched for the date of the operation in keeping with the learning curve.

Results: The study group comprised 26 (37 per cent) males and 44 (63 per cent) females with a mean age of 58·5 years and the control group was well matched. In both groups 73 per cent of the operations were performed by a single consultant surgeon. A mean operative time of 76·5 min and 54·5 min were recorded for the study and the control groups, respectively ($P<0\cdot0001$). Operative difficulty was noted in 58·5 per cent compared with only 24 per cent of the control group. The conversion rates were 17 per cent and 6·8 per cent in the study and control groups, respectively. The mean postoperative stay was 4·3 days (range 1–48 days) compared with 2·16 days (1–13 days) in the control group ($P<0\cdot003$). The analgesic requirement was found to be significantly higher in the study group.

Conclusion: This study clearly shows that patients with biliary tract disease who required preoperative ERCP had more difficult laparoscopic cholecystectomies together with increased conversion rates, operating times, postoperative hospital stay, complication rates and analgesic requirements. Preoperative identification of a difficult LC would enable one to institute a safe management plan.

H & P 009

Management of primary hepatocellular carcinoma in a specialist hepatobiliary centre

K.K. Singh, S.J. Wigmore, E. Currie, K.K. Madhavan,
D.N. Redhead and O.J. Garden *University Department of Surgery, Royal Infirmary of Edinburgh, Edinburgh*

Background: The aim of this study was to assess the management and outcome of patients presenting with hepatocellular carcinoma at a tertiary referral centre.

Method: One hundred and seven consecutive patients (male 69 per cent, median age 62 years) with the diagnosis of hepatocellular carcinoma were audited prospectively between 1988 and 1997. Patients were clinically assessed and staged with computed tomography scan, ultrasound, angiogram, and laparoscopy with intraoperative ultrasonography.

Results: Following assessment, 34 patients (32 per cent) were considered unsuitable for any intervention, 56 patients (52 per cent) underwent chemo-embolization and 17 (16 per cent) underwent resectional surgery. There was one postoperative death in a cirrhotic patient (mortality 5·8 per cent). The median survival for these patients was 40·7 months (95 per cent CI range = 19·7–61·6). The overall 5-year survival for all patients was 6 per cent. At 2 years from diagnosis, marked differences were observed in the survival, with estimates of 83 per cent for resections, 23 per cent for chemo-embolization and 11 per cent for those who had no treatment (log rank $P<0\cdot00001$). Elevation of serum gamma glutamyl transferase ($R=0\cdot2$, $P<0\cdot03$) and alkaline phosphatase ($R=0\cdot2$, $P<0\cdot03$); presence of vascular invasion ($R=0\cdot3$, $P<0\cdot009$), presence of distant metastases ($R=0\cdot2$, $P<0\cdot05$), and increasing number of hepatic segments involved by tumour ($R=0\cdot2$, $P<0\cdot05$), correlated with poor survival.

Conclusion: Resectability of hepatocellular carcinoma remains low at 16 per cent and the overall survival is poor. It is important, however, that these patients are assessed and staged by a specialist surgical hepatobiliary unit and appropriate treatment modality is employed as this may result in a significant survival benefit for some patients.

Coloproctology 1–9 Thursday 14 May, 14·30–16·00

Coloproctology 001

Randomized controlled trial of metronidazole to reduce pain after day-case haemorrhoidectomy

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Background: The aim of this study was to investigate the effect of metronidazole on postoperative pain after day-case haemorrhoidectomy (DCH).
Method: Forty consecutive patients (17 male) aged 36–65 years (mean 49) randomly received metronidazole ($n=20$) or placebo in a double-blind manner. All received lactulose 2 days preoperatively. Diathermy haemorrhoidectomy was performed with no anal canal dressing. Patients were discharged on the same day and given diclofenac, 0·2 per cent glycerine trinitrate ointment, lactulose, a contact bleep number, and early outpatient review. Additional analgesics were used as required and patients completed questionnaires for pain, expectation of pain and satisfaction.
Results: Overall, patients experienced less pain than expected, except on days 3 and 4. Patients using metronidazole had significantly less pain on days 5, 6 and 7 compared to placebo ($P<0{\cdot}01$, $P=0{\cdot}02$ and $P<0{\cdot}01$). Nine patients on metronidazole used additional analgesia compared to 13 on placebo ($P=0{\cdot}34$). Return to work was significantly earlier ($P=0{\cdot}01$) with metronidazole (15 days) compared to placebo (18 days). There were two re-admissions (both on placebo), one for faecal impaction, the other secondary haemorrhage. Patient satisfaction was higher in the metronidazole group at weeks 1 ($P=0{\cdot}005$), and 6 ($P=0{\cdot}06$).
Conclusion: Prophylactic metronidazole assists DCH by suppressing secondary pain around days 5 to 7 leading to high patient satisfaction and earlier return to work.

Coloproctology 002

Proinflammatory effects of colitic mucosa on neutrophil adhesion

I.E. Nichol, S.M. Plusa, C. Marshall, J. Kirby, B.K. Shenton and J.S. Varma *Department of Surgery, University of Newcastle upon Tyne, Newcastle upon Tyne*

Background: To investigate the functional effects of inflammatory mediators produced by mucosal biopsies from patients with ulcerative colitis on neutrophil–endothelial interactions.
Method: Conditioned medium (CM) from incubated colitic and control mucosal biopsies was added to whole blood from a healthy donor. Expression of the neutrophil adhesion receptor CD11b and neutrophil-endothelial adhesion was determined by flow cytometry.
Results: Incubation with colitic CM produced significantly greater CD11b expression after 5 ($P=0{\cdot}004$), 15 ($P=0{\cdot}024$) and 30 min ($P=0{\cdot}025$) than controls. Neutrophil–endothelial adhesion ratio was significantly greater with colitic biopsies than controls ($P=0{\cdot}0052$).
Conclusion: Mucosal biopsies from patients with ulcerative colitis produce soluble mediators that activate neutrophils and promote neutrophil–endothelial adhesion.

Coloproctology 003

A prospective randomized trial of total intravenous anaesthesia with epidural or opiate analgesia in elective colorectal surgery

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North Tees General Hospital, Stockton-on-Tees, Cleveland

Background: The aim of this study was to compare differing anaesthetic and analgesic techniques on peri-operative outcomes of colorectal surgery.
Method: In this prospective randomized trial, 35 patients so far have been entered into four treatment arms. All received trial of total intravenous anaesthesia (TIVA) and either inhaled nitrous oxide/oxygen mixture or air/oxygen. Peroperatively patients received either intravenous morphine or epidural bupivacaine, analgesia, maintained postoperatively as patient-controlled analgesia (PCA) or by continuous epidural infusion.
Result: Peroperatively, patients who had epidurals tended to have less operative blood loss (median 780, range 200–2625 ml) than the morphine group (median 1425, range 250–2725 ml) and fewer of them were transfused postoperatively (24 per cent vs 61 per cent; $P<0{\cdot}05$). Pain relief, measured subjectively (defined as excellent/good or fair/poor) was significantly better in those who had an epidural (83 per cent vs 44 per cent; $P<0{\cdot}005$). Return of intestinal function was assessed by measuring days to return of bowel sounds, first flatus and first bowel action with trends suggesting an advantage to the epidural group. The time to full mobility postoperatively was also less in the epidural group and in particular the patients who had epidural/nitrous oxide (median 4·6 days vs 6·0 days).
Conclusion: The use of epidurals for colorectal surgery is associated with a reduction in blood loss, transfusion requirements, gives superior pain relief and may afford earlier return of intestinal function and mobility.

Coloproctology 004

The strength–duration curve combined with manometry of the external anal sphincter: a powerful assessment of neuromuscular integrity?

D.N. Monk, P. Mills, J. Jeacock, M. Deakin, A. Cowie and E.S. Kiff *University Hospital of South Manchester, Wythenshawe, Manchester*

Background: The strength–duration curve of a muscle is thought to be a measure of its innervation. This study evaluates manometry and the strength–duration curve of the external anal sphincter for discriminating between controls and patients with faecal incontinence.
Method: Forty-three female patients with disordered defaecation, predominantly incontinence were studied along with 45 age-matched females with no disorders of defaecation. A full lower gastro-intestinal history, strength–duration curve of the external anal sphincter, ano-rectal manometry and pudendal nerve terminal motor latency were recorded.
Results: Logistic regression was performed using resting and voluntary squeeze pressure and current strengths at 28 different pulse durations to develop a predictive equation for group membership. It was found that only the currents at 1 and 6 ms were significant predictors of group membership. When ano-rectal manometry data were included only the current required to elicit contraction at 1 ms was required. The following regression equation can be applied to predict continence in this population with a sensitivity of 95 per cent and specificity of 100 per cent. A negative value indicates continence.
$\mathrm{Logit}\ (P) = 4{\cdot}1605 - 0{\cdot}0559 \times \text{Squeeze pressure} - 0{\cdot}1755 \times \text{Resting pressure}\ 0{\cdot}86221_{\mathrm{Ams}}$
Conclusion: These data show that data from the strength–duration curve can be used in conjunction with ano-rectal manometry to produce a powerful discriminatory tool for faecal incontinence. This simple and inexpensive technique may have a role in evaluation of the neuromuscular integrity of the anal sphincter in the investigation of patients with faecal incontinence.

Coloproctology 005

Outcome following perianal fistula surgery: predictive value of magnetic resonance imaging

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Background: The aim of this study was to assess the ability of preoperative magnetic resonance imaging (MRI) to predict clinical outcome following surgery of perianal fistulas.

Method: A cohort of 37 patients with active perianal fistulas was assessed by MRI with the dynamic contrast-enhanced technique. This was performed prior to surgical exploration and management as part of a prospective blinded study. Outcome for this cohort was assessed at a minimum of 1 year after surgical exploration. Outcome was then correlated in a blinded fashion with the surgical and magnetic resonance (MR) grading of the severity of the fistulous disease.

Results: MRI was better than surgical exploration at predicting outcome (MRI positive predictive value (PPV) 73 per cent, negative predictive value (NPV) 87 per cent, sensitivity 89 per cent, specificity 68 per cent; surgical exploration PPV 57 per cent, NPV 64 per cent, sensitivity 73 per cent, specificity 47 per cent). MR classification of fistulas was significantly associated with outcome ($P = 0{\cdot}0004$) and surgical classification was not significantly associated ($P = 0{\cdot}22$) with outcome (χ^2 test). There was a significant difference between the MR grades of patients with satisfactory and unsatisfactory outcomes ($P < 0{\cdot}001$, Mann–Whitney U-test).

Conclusion: As well as accurately determining the surgical anatomy of perianal fistulae MRI better predicts clinical outcome than surgical exploration. Dynamic contrast-enhanced MRI is of value in the management of perianal fistulas.

Coloproctology 006

Pre-operative radiotherapy for rectal cancer: who needs it?

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Background: Adjuvant preoperative radiotherapy has been advocated for all patients with rectal cancers in an attempt to reduce local recurrence. This approach leads to over-treatment and toxicity in the majority of patients who are not at risk of local recurrence.

Method: We reviewed 114 consecutive patients who presented with rectal cancer under the care of a single surgeon over a 5-year period. Follow-up was for a minimum of 2 years. Patients were placed in palliative or curative groups preoperatively on the basis of a pelvic computed tomography scan or examination under anaesthesia. Preoperative radiotherapy was offered to patients with locally advanced tumours.

Results: Of these 114 patients, 78 underwent anterior resection; 36 patients with tumours >10 cm from the anal verge underwent anterior resection with a handsewn anastomosis. Sixty-six patients with tumours <10 cm from the anal verge underwent total mesorectal excision (TME) with a double stapled coloanal anastomosis in 42 patients, and an abdomino-perineal resection in 24 patients. There was one perioperative death (0·8 per cent) and three anastomotic leaks. Seventy-three per cent of operations were considered curative on the basis of preoperative staging. Of these, three (3·9 per cent) went on to develop local recurrence and 10 patients (13·1 per cent) developed disseminated disease. In the palliative group, 14 (44 per cent) patients had preoperative evidence of locally advanced disease. Of these, 10 (71 per cent) died within 1 year due to advanced disease or local recurrence. All four patients who did not develop local recurrence had lateral resection margins which were free of tumour.

Conclusion: These data suggest that preoperative staging can predict with accuracy those patients at risk of developing local recurrence and preoperative adjuvant therapy can therefore be restricted to this group.

Coloproctology 007

Can simple delivery data predict the likelihood of an obstetric anal sphincter injury?

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Background: Anal sphincter injury is recognized in relation to childbirth. Previous authors are inconclusive as to which delivery variables are associated with such damage and may be useful in predicting its occurrence.

Method: A prospective study was undertaken to determine whether baby weight, head circumference, length of second stage and active pushing could be correlated to occurrence of anal sphincter injury. One hundred and fifty-nine women delivering at a single unit were assessed using anal endosonography and delivery data were evaluated to see if a statistically significant difference existed in the presence of sphincter trauma.

Results: There were no third-degree tears in the group; endosonography revealed sphincter disruption in 8·7 per cent of those delivering normally and in 83 per cent of those requiring forceps. No correlation was detected between any of these variables and the presence of sphincter injury (Mann–Whitney U-test and Spearman correlation).

Conclusion: Besides forceps delivery, delivery variables previously perceived as potential predictors of sphincter injury are not useful in predicting its occurrence. With a low incidence of sphincter injury in normal deliveries routine postnatal assessment is not warranted but should be mandatory for all instrumental deliveries.

Coloproctology 008

The effect of direct electrical stimulation on the intact colon

A. Maw, M-A. Pilot, M.R. Hutton, A.J.P. Eccersley, A. Basu, M. Scott and N.S. Williams *Academic Department of Surgery, St Bartholomew's and the Royal London School of Medicine and Dentistry, Queen Mary and Westfield College, London*

Background: Colonic dysmotility caused by intrinsic abnormalities or following surgery may result in ineffective rectal evacuation. Electrical stimulation has been shown to produce contractions in isolated colonic smooth muscle and isolated colonic pouches but there are no studies investigating its potential to produce propulsive contractions in the intact colon.

Method: Experiments were performed on nine (20 kg) pigs under general anaesthesia. At laparotomy, a DS7 constant current stimulator delivered pulsed, monophasic, square wave impulses, of 2 min duration, to pairs of bi-polar stainless steel electrodes positioned within the muscularis propria at the caecal pole (CP) and opposite the ileocaecal valve (ICV). Serosal strain gauges recorded smooth muscle activity. Intraluminal responses to stimulation were measured using a compliant balloon connected to a barostat and by solid-state pressure transducers.

Results: The threshold current and pulse width relationship was exponential and maximum contractile response occurred with a stimulus of 10 Hz, 2 ms, 100 mA. Median unstimulated intraluminal pressure was 3·4 mmHg (range 1·1–5·6). Maximal stimulation between CP electrodes caused localized, non-propagated contractions [median pressure rise 4·1 mmHg (range 2·1–13·3)] whereas cross stimulation between CP and ICV electrodes caused mass caecal contraction [median pressure rise 10·5 mmHg (range 5·3–13·3) $^{*}P = 0{\cdot}006$]. A dose–response curve for contractile amplitude was seen with alterations in current and pulse width. Stimulation produced reductions in caecal volume of up to 100 per cent, changes being greater with cross caecal stimulation at any given inflation pressure of the barostat balloon (Table).

	Median percentage reduction in barostat balloon volume (range)		
Barostat pressure	ICV to CP electrode (range)	CP electrode pair (range)	Probability
5 mm Hg	72 (15–100)	22 (4–50)	$^{*}P = 0{\cdot}002$ ($n = 12$)
10 mm Hg	45 (19–64)	13 (4–45)	$^{*}P = 0{\cdot}002$ ($n = 12$)
15 mm Hg	21 (16–27)	7 (4–9)	$^{*}P = 0{\cdot}18$ ($n = 2$)

* = Wilcoxon matched pairs signed rank test

Conclusion: Electrical stimulation of the intact porcine caecum generates propulsive contractions capable of producing evacuation at physiological intraluminal colonic pressures. This has a number of potential applications in the treatment of disorders of colorectal evacuation and in total anorectal reconstruction.

Coloproctology 009

Long-term function of the electrically stimulated gracilis neosphincter

A.J.P. Eccersley, A. Maw and N.S. Williams *Academic Department of Surgery, Queen Mary and Westfield College, London*

Background: Most reports of the electrically stimulated gracilis neosphincter (ESGN) describe only short-term outcome, with little information available on longer-term continence. This study aimed to assess function and physiology in patients who had an ESGN constructed more than 5 years ago.
Method: Records of all 31 patients who underwent an ESGN from 1988–92 for intractable faceal incontinence or as part of total anorectal reconstruction were reviewed. The 14 patients who retained the ESGN for more than 5 years were identified and their long-term continence, anorectal physiology and electrical stimulation parameters were assessed.
Results: After a median follow-up of 80 (range 50–107) months from stoma closure, Cleveland clinic continence scores improved from 20 (16–20) preoperatively to 8 (2–14) at 5 years. The batteries of nine prototype stimulators became depleted, of which three were replaced once and three twice, giving a median battery life of 35 (9–80) months. Over 5 years median stimulation threshold increased from 0·75 V (0·3–3) to 1·2 V (0·4–7·0) but sphincter function remained satisfactory with median resting and squeeze pressures 21 (10–40) and 54 (35–90) cm H_2O. Survival curve analysis revealed that long-term continence was most likely in patients treated for traumatic anorectal injuries, and was more likely in those who had an Alpha (nine out of 16 after 5 years) rather than a Gamma (three out of 14) wrap.
Conclusion: Long-term continence and sphincter function can be obtained with the ESGN, despite episodes of battery depletion.

Vascular 1–11

Thursday 14 May, 14·30–16·00

Vascular 001

The fate of patients undergoing surveillance of small abdominal aortic aneurysms

R.B. Galland, M.S. Whiteley and T.R. Magee *Royal Berkshire Hospital, Reading*

Background: Increasing numbers of patients with small abdominal aortic aneurysms (AAA) are being diagnosed. The aim of this paper is to define the fate of those patients undergoing surveillance of small AAAs.
Method: A prospective study has been carried out of all patients undergoing surveillance. At the time of the first consultation the patient was assessed, a Detsky score calculated and the referral source noted. End points of the study were elective repair of the aneurysm, aneurysm rupture or death of the patient.
Results: Details of 267 patients were analysed. The referral source was general practitioner in 39 per cent, patients with peripheral vascular disease in 32 per cent and department of urology in 21 per cent. No patients were referred from population screening. The cumulative 5-year risks of rupture, elective repair or non-AAA-related deaths were 15 per cent, 26 per cent and 46 per cent for all patients, 4 per cent, 13 per cent and 38 per cent for patients initially presenting with AAA of <4 cm diameter and 21 per cent, 42 per cent and 54 per cent for patients presenting with an AAA of 4–5·5 cm diameter. All but one of 11 patients whose aneurysm ruptured were unfit or had declined elective repair. There were 56 non-AAA-related deaths, the majority due to cardiovascular causes. Those patients with low Detsky scores had a 5-year survival of 62 per cent, those with high scores 44 per cent. The age/sex-matched survival of a normal population at 5 years is 80 per cent.
Conclusion: Overall the non-AAA-related mortality was greater than the risks of rupture or elective repair. It is important to bear in mind the poor prognosis of this group of patients compared with a normal population when considering elective repair of small AAAs.

Vascular 002

Growth rate of abdominal aortic aneurysms: how frequently should they be scanned?

P.S. Basnyat, S. Chawda, E. Morgan*, E. Townsend, R.K. Winter and M.H. Lewis *East Glamorgan General Hospital and *University of Glamorgan*

Background: There is no agreed consensus on how often a patient should be followed-up once an abdominal aortic aneurysm (AAA) is detected. The aim of this study was to assess growth rate of AAA on our follow-up programme and to determine the current protocol needed modification.
Method: We have been running an AAA screening programme for hypertensives since 1994. All patients followed-up for AAA by ultrasound between 1994–1996 were included. Those with only one scan were excluded from the study. Our current protocol is annual ultrasound scan for AAA less than 3·9 cm and scans at intervals of 6 months for aneurysms greater than 4 cm.

AAA size (cm)	Number of patients	Sex		Mean age (years)	Mean growth (cm/year)	Maximum growth (cm/year)
		Male	Female			
<2·9	32	25	7	73	0·07	0·38
3–3·4	63	49	14	71	0·15	0·6
3·5–3·9	38	30	8	73	0·17	0·8
4–4·4	22	20	2	72	0·21	1·1
4·5–4·9	11	8	3	79	0·23	0·45
>5	5	4	1	74	0·29	0·56

Conclusion: Maximum growth rate of AAA in each group should be considered when deciding on scanning intervals. We suggest an abdominal aorta of less than 2·9 cm should be scanned every 3 years, 3–3·4 cm at intervals of 2 years, 3·5–3·9 cm annually and those above 4 cm should be scanned every 6 months.

Vascular 003

Intravascular ultrasound in stenting for aortic occlusive disease

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Background: Intravascular ultrasound (IVUS) allows assessment of endoluminal and vascular wall morphology. The role of IVUS as a tool in assessment of aortic stent placement and follow-up, for occlusive disease, was investigated and compared to angiography.
Method: IVUS was carried out using a mechanical rotating head system with either a 30 MHz Dumed, or a 20 MHz CVIS system. The IVUS catheter was introduced percutaneously by retrograde femoral route prior to carrying out imaging. Aortic diameter at, above and below the site of the lesion was measured. Balloon size and endovascular stent were selected on the basis of IVUS measurements, and guided under fluoroscopic control to the lesion site. The stent was placed under fluoroscopic control. After placement, the stent was imaged by IVUS.
Results: IVUS was used to assess 13 stents (12 Palmaz and one Nitinol Memotherm) placed for severe symptomatic ischaemia of the lower limbs in nine patients (five male, four female; age range 57–80 years). Eight stents were imaged at time of placement and five at follow-up when patients developed recurrent symptoms of ischaemia. In all cases following balloon angioplasty under fluoroscopic control, IVUS revealed under-expansion of the stent (mean 3 ± 0·9 mm), compared to angiography, necessitating further angioplasty. Maximum balloon diameter was 14 mm and stent expansion ranged from 10–12·85 mm. Symptomatic recurrence was found to be due to thrombus formation, stent irregularity and under-expansion.
Conclusion: IVUS demonstrates that stent under-expansion is a common phenomenon in large-sized stents placed for aortic occlusive disease. This factor may be significant in recurrent problems following endovascular stenting.

Vascular 004

A comparison of mortality in screened and non-screened patients undergoing elective aortic aneurysm repair

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Background: The main benefit of abdominal aortic aneurysm (AAA) screening should be derived from the differences in the mortality between elective and ruptured AAA repair. The aim of this study was to compare the mortality rates for elective repair in screened and non-screened detected AAAs.
Method: Patients undergoing elective AAA repair were either from a current screening programme to detect men over 65 years with AAAs (screened), or were referred from other sources (non-screened). Aneurysms presenting acutely but having non-urgent surgery were included. Mortality data relating to these patients were studied.
Results: Three hundred and twenty-eight aneurysm repairs were performed with a median of 45 repairs per annum (range 32–62) and with an overall mortality of 6·4 per cent. The yearly data for number of operations and mortality are shown for the screened, non-screened and total county populations. The proportion of screened operations rose with time but there was no increase in the total number performed.

	1991	1992	1993	1994	1995	1996	1997	Total/% mortality
Number								
Screened operations	11	10	13	23	19	36	18	130
Non-screened operations	38	22	26	39	26	28	19	198
County	49	32	39	62	45	64	37	328
Mortality								
Screened operations	1	0	0	0	3	2	0	6* (4·6%)
Non-screened operations	5	2	2	2	2	2	0	15* (7·6%)
County	6	2	2	2	5	4	0	21* (6·4%)

*χ^2 test, P=N.S.

Conclusion: Screened patients had a similar mortality to non-screened patients for AAA repair. The screening programme has not increased the annual cost of elective repair of AAA as, despite increasing numbers of screened operations, the total number of AAA repairs performed per annum has not increased.

Vascular 005

Fast contrast-enhanced magnetic resonance angiography of the aorta and lower extremity vessels using a novel approach

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Background: The aim of this study was to develop an approach for magnetic resonance imaging (MRI) of the aorta and lower extremity vessels using fast contrast-enhanced magnetic resonance angiography (MRA).
Method: We devised a novel approach for contrast-enhanced MRI of the aorta and lower extremity vasculature by moving the table on which the patient lies between three successive imaging acquisitions centered over the aorto-iliac, femoro-popliteal and below-knee segments, thus allowing imaging over a sufficiently large region of interest. Digital image subtraction was employed to improve image quality. Twenty patients with intermittent claudication underwent both conventional catheter angiography and gadolinium-enhanced MRA with this new technique at 1·5 Tesla of the aorta and outflow vessels.
Results: Compared to catheter arteriography MRA had 95 per cent sensitivity and 98 per cent specificity for demonstration of occlusions, but MRA confirmed patency of numerous segments thought to be occluded using the conventional method. There was good interobserver correlation between the two readers overall with a weighted kappa of 0·834 for all lesions, kappa 0·861 for reporting of insignificant (<50 per cent) stenoses compared to significant (>50 per cent) ones, and kappa 0·917 for reporting of occluded vs patent (0–99 per cent stenosis) segments.
Conclusion: This technique shows high accuracy compared to catheter arteriography in patients with occlusive arterial disease of the aorta and outflow vessels. Our preliminary results suggest that this technique may ultimately provide a safe, non-invasive and cost-effective alternative to catheter arteriography.

Vascular 006

Renal artery stenosis: the significance of its incidental finding on peripheral angiography

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Background: As more angiograms are being performed for lower limb ischaemia renal artery stenosis (RAS) is increasingly diagnosed as an incidental finding. We aimed to determine the prevalence of RAS in patients with peripheral vascular disease and its impact on patient outcome.
Method: All peripheral angiograms performed over a 2-year period were independently reviewed to determine the degree of RAS. Those patients found to have RAS of 50 per cent or more were then studied further. Mortality risk factors were recorded and statistical analysis performed using χ^2 tables with Yates' correction. Follow-up was available for a minimum of 2 years and a maximum of 4 years.
Results: Analysis of 1102 consecutive angiograms revealed 156 (14·2 per cent) patients with RAS. In this group there was a high overall mortality rate of 21·2 per cent. Hypertension and diabetes were common, 62·7 per cent and 20·6 per cent respectively, while elevated serum creatinine >130 µmol/l was found in 10·9 per cent. Bilateral or severe unilateral stenosis >90 per cent was identified in 43·6 per cent. However the only risk factor useful in identifying a high mortality subgroup was elevated baseline creatinine (P=0·004, two-tailed t-test).
Conclusion: We conclude that the prevalence of RAS merits flush aortography to visualize the renal arteries in all patients undergoing peripheral angiography. Furthermore, any patient with pre-existing elevation of creatinine and RAS is at exceptionally high-risk and merits urgent investigation of renal and cardiac function.

Vascular 007

A prospective study of internal carotid artery plication during carotid endarterectomy: early clinical and duplex outcome

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Background: It has been suggested that the internal carotid artery (ICA) should be plicated during carotid endarterectomy (CEA) in order to exclude the distal intimal step and/or shorten the ICA, thus preventing turbulence and kinking. The aim of this study was to examine the early clinical and duplex outcome of patients undergoing CEA with plication.
Method: Analysis of a prospectively gathered computerized database comprising operative and clinical and duplex follow-up data pertaining to 212 consecutive CEAs performed between 1 November 1992 and 31 July 1997.
Results: Sixty patients (median age 68 years, range 49–85 years) undergoing 62 CEAs also had ICA plication because, in the opinion of the senior operator, the distal intimal step required 'tacking' down and/or there was a risk of postoperative kinking due to ICA redundancy. The plication technique will be described. Indications for CEA were transient ischaemic attack (TIA) 46 per cent, amaurosis fugax 19 per cent, TIA and stroke 13 per cent, TIA and amaurosis 11 per cent, and asymptomatic disease 11 per cent. All but one patient underwent patch angioplasty. There was one intraoperative stroke which was fatal (combined stroke and death rate 1·6 per cent) and two (3·2 per cent) transient ischaemic attacks. There was no other major morbidity and no patient suffered perioperative carotid thrombosis. Forty-six patients underwent postoperative duplex scan surveillance for a median of 12 (range 1–36) months: no abnormality was detected in 87 per cent; 9 per cent had restenosis <50 per cent and 4 per cent had restenosis 50–75 per cent. All restenoses were asymptomatic.
Conclusion: ICA plication is a useful, quick and technically straightforward means of excluding the distal intimal step and straightening the ICA. Plication avoids the need for arterial division or resection and does not adversely affect early clinical or duplex outcome after CEA.

Vascular 008

To compare clinical outcomes, length of stay and complications of local versus general anaesthetic for carotid endarterectomy

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Background: The aim of this study was to review and compare the major and minor complication rates, length of stay, number of therapeutic interventions and outcomes of two cohorts of patients undergoing carotid endarterectomy for symptomatic carotid stenosis.

Method: One hundred patients, 50 under general anaesthetic (GA) and 50 under local anaesthetic (LA), prospectively entered on to a carotid endarterectomy database, were retrospectively reviewed with reference to complication rate, blood pressure control, use of shunt, length of stay, therapeutic interventions and clinical outcome. For GA patients, shunts were inserted when the transcranial Doppler-assessed blood flow fell by >50 per cent. For LA patients, shunts were inserted for clinical neurological deficit. All patients were subject to on-table duplex scanning and subsequent vascular studies follow-up.
Results: There were no significant differences in stroke/death rates. No patient undergoing LA required a GA. There were no differences in minor complications (haematoma, transient nerve damage, transcranial ischaemic attack). Blood pressure control was significantly more stable in LA patients. Therapeutic interventions were a mean of six episodes for GA patients and one episode for LA patients. Length of stay was 2–3 days for GA and 1–2 for LA. There were no delayed complications related to early discharge and no differences in clinical outcome or restenosis at 2 months. Longer follow-up is awaited.
Conclusion: Carotid endarterectomy under LA seems to be a safe and effective method of performing the operation; it is associated with fewer therapeutic interventions, a more stable and faster recovery and shorter length of stay than GA.

Vascular 009

Carotid endarterectomy without angiography does not compromise outcome

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Background: Carotid angiography is associated with a 2 per cent risk of stroke and since the advent of colour duplex ultrasound, its role in the assessment of patients with carotid disease has been the subject of debate. The aim of this study was to evaluate a 5-year experience of carotid endarterectomy without routine angiography.
Method: A prospective audit of the results of carotid endarterectomy without routine angiography from January 1992 to December 1996. Angiography was performed only if the ultrasonographer was concerned about the distal or proximal extent of disease or to assess subocclusion.
Results: During the study period, 470 carotid endarterectomies were performed. Only 35 patients underwent carotid angiography. The indications for angiography were subocclusion in 22 patients, to assess the extent of proximal/distal disease in 12 and abnormal anatomy in one. Throughout the study period the overall perioperative death and/or stroke rate was 4·2 per cent. In 1997, the perioperative stroke rate had fallen to 1·3 per cent. In no case was the operation abandoned due to unexpected findings.
Conclusion: Although concerns exist about the precise duplex criteria for diagnosing a severe stenosis, this study has shown that a policy of selective angiography does not compromise patient safety or operability and avoids the unnecessary mortality, morbidity and costs associated with routine angiography.

Vascular 010

Endovascular stenting and traumatic aneurysms of the internal carotid artery

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Background: The aim of this study was to assess our experience in the management of pseudoaneurysms of the internal carotid artery using endovascular stenting.
Method: Retrospective analysis of recent experience at one teaching hospital.
Results: Three young patients aged 19, 28 and 39 years presented with false aneurysms of the carotid artery. All three lesions arose as a result of road traffic accidents. At initial presentation, two patients had an ipsilateral stroke and all three had variable palsies of cranial nerves IX, X, XII and/or Horner's syndrome. One patient had bilateral carotid artery aneurysms. Intervention was indicated in order to prevent the development of a further stroke. All three lesions were treated by endovascular stent placement introduced via a femoral arterial puncture. In one patient, tungsten coils were also placed within the aneurysm sac. All three false aneurysms were completely excluded and there were no procedure-related complications. During the follow-up period (2, 3 and 28 months) the lesions have remained excluded with continued carotid artery patency and no further neurological symptoms.
Conclusion: Our early experience encourages us to continue with this technique, supplemented with careful follow-up as little is known about the optimum choice of stent.

Vascular 011

Carotid endarterectomy: practice and outcome before and after ECST and NASCET

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Background: The European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET), published in 1991, demonstrated the benefit of carotid endarterectomy (CEA) in patients with high-grade symptomatic internal carotid artery stenosis. This study examines changes in practice and outcome of CEA before and after publication of these trial data.
Method: Analysis of a computerized database gathered 557 primary CEAs performed between January 1975 and October 1997. Two time periods are compared.
Results: Although clinical indications for CEA have not significantly changed, operated patients now represent a higher risk group in terms of co-morbidity, presence of infarct on computed tomography and severity of arterial disease. There has been a significant increase in the use of shunting and patch angioplasty. The proportion of patients operated for asymptomatic disease remains small.

	1975–1991 $n=260$ (%)	1992–1997 $n=297$ (%)	P value (Fisher's exact test)
Amaurosis fugax/retinal artery occlusion	102/13	107/12	NS
Transient ischaemic attack	161	165	NS
Preoperative stroke (recovery/persistent deficit)	34/39	43/52	NS
Asymptomatic	12	22	NS
Established hypertension	98 (38)	153 (52)	<0·005
Diabetes	15 (6)	32 (11)	<0·05
Infarct on preoperative CT	55/170 (32)	72/144 (50)	<0·005
Operated stenosis > 75%	74 (28)	220 (74)	<0·0001
Shunt used	72 (28)	108 (36)	<0·03
Patch angioplasty	168 (65)	247 (83)	<0·0001
Total perioperative neurological event rate	30 (11·5)	17 (5·7)	<0·02

Conclusion: Since ECST and NASCET there has been a four-fold increase in the numbers of CEA performed annually. Despite operating on higher risk patients there has been a significant and continuing reduction in perioperative morbidity.

Breast 1–9 Thursday 14 May, 14·30–16·00

Breast 001

Serum VEGF in breast cancer: relationship with stage, type and receptor status

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Background: Vascular endothelial growth factor (VEGF), is one of the most potent angiogenic cytokines. Tumour levels correlate with micro vessel density, nodal metastasis and disease-free survival. This study evaluates the relation between serum VEGF and various pathological indices of breast cancer.
Method: Serum VEGF165 was assayed preoperatively in 135 patients with breast cancer and compared to serum VEGF levels in 72 healthy women. All tumours were staged by a single pathologist according to the TNM classification.
Results: Serum VEGF was elevated in all stages of breast cancer. Levels in nodal, recurrent and metastatic disease were significantly higher than controls. Patients with ductal carcinoma *in situ* (DCIS) had elevated levels compared to controls. Elevated VEGF levels were observed in 67·5 per cent of patients compared to 11·2 per cent patients with raised CA15-3 and 13 per cent with abnormal CEA levels.

	Median (IQR) VEGF pg/ml	P (value vs controls)
Controls ($n=72$)	173·8 (92·5–252·5)	
DCIS ($n=8$)	450·4 (301·8–795·2)	$P=0{\cdot}002$
Ductal carcinoma ($n=95$)	307·7 (155·5–483·0)	$P<0{\cdot}0005$
Lobular carcinoma ($n=16$)	207·1 (118·7–379·8)	$P=0{\cdot}32$
ER positive ($n=62$)	305·9 (179·7–485·2)	$P=0{\cdot}0005$
ER negative ($n=20$)	267·8 (94·2–523·7)	$P=0{\cdot}1$

VEGF levels were not significantly elevated in patients with lobular cancer or those with ER-negative tumours.

Conclusion: Serum VEGF shows a correlation with not only tumour stage and cancer cell type, but also with oestrogen receptor (ER) status. This may have implications in the study of hormones in the aetiology, pathogenesis and prognosis of breast cancer. Serum VEGF is more sensitive than currently employed tumour markers and it may have a role in monitoring disease prognosis in breast cancer patients.

Breast 002

Comedo ductal carcinoma *in situ*: anti-oestrogen therapy does not increase apoptosis nor decrease proliferation

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Background: Over 50 per cent of screen-detected ductal carcinoma *in situ* (DCIS) lesions are of the comedo subtype which are usually oestrogen receptor-negative. The value of postoperative anti-oestrogen (AE) therapy in preventing recurrence following breast conserving surgery for DCIS is currently under evaluation in two national trials. Using an *in vivo* model for human DCIS, the effect of E_2 and AE treatment on programmed cell death (apoptosis) and cellular proliferation (Ki67 immunoreactivity) in DCIS lesions was examined.
Method: In each of 20 experiments, a median of 16 athymic nude mice (range 12–20) were implanted with eight DCIS xenografts per mouse and given either no treatment, a subcutaneous slow release 2 mg β-oestradiol pellet (E_2) or a weekly injection of 0·1 ml Faslodex^{TM} (a pure AE) for 2 weeks. Xenografts were then removed and apoptotic and Ki67 indices compared between treatment groups by examining cell morphology on H&E sections (no. cells exhibiting apoptosis/total no. cells counted) or by immunohistochemistry (Ki67 proliferation index).
Results: All non-comedo lesions and three of 15 comedo DCIS lesions were oestrogen receptor-positive. Pretreatment apoptotic and proliferative rates were significantly higher in comedo than non-comedo lesions ($P<0{\cdot}001$ and $P=0{\cdot}02$ respectively). E_2 or AE therapy had no significant effect upon comedo DCIS whereas in non-comedo DCIS E_2 treatment resulted in increased proliferation ($P=0{\cdot}03$) and apoptosis ($P=0{\cdot}006$) whilst AE treatment resulted in increased apoptosis alone ($P=0{\cdot}04$) compared to controls.

	Comedo DCIS ($n=15$)		Non-comedo DCIS ($n=5$)	
Median (range)	Apoptotic index	Ki67 index	Apoptotic index	Ki67 index
Pretreatment	1·6% (0·7–3·7)	16·2% (7–46)	0·4% (0·1–0·6)	2·2% (0–16)
Control group	1·4% (0–3·5)	16·9% (2–29)	0·4% (0·1–1·7)	7·0% (2–21)
E_2 group	1·3% (1·7–2·6)	17·5% (7–46)	1·5% (0·3–2·3)	10·5% (6–31)
Anti-oestrogen group	0·8% (0·4–3·6)	14·8% (14–18)	1·0% (0·5–2·0)	8·1% (4–11)

Conclusion: Non-comedo DCIS (usually ER positive) is responsive to hormonal manipulation but women with comedo DCIS (usually oestrogen receptor-negative) are unlikely to benefit from AE therapy and other therapeutic strategies need to be investigated.

Breast 003

The specialist treatment of the axilla

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Background: Previous reports have highlighted both the survival advantage of treatment by larger specialist breast units and also the poorer survival associated with inadequate axillary treatment for breast cancer. This report compares the adequacy of treatment of the axilla by specialists and non-specialist units and the outcome of this treatment.
Method: All 7144 histologically confirmed invasive breast cancers in women under 75 diagnosed from 1980 to 1994 who lived in a defined geographical area (population 1·5 million) were identified and the original pathology reports and 1950 out of 2531 case records for the years 1986–1991 obtained. The cause of death was derived from death certificate data.
Results: Specialists compared to non-specialists performed no axillary surgery in 448 (19 per cent) vs 1705 (36 per cent); inadequate sampling in 136 (6 per cent) vs 1013 (14 per cent); sampled 4–9 nodes in 927 (39 per cent) vs 2301 (32 per cent); and 10+ nodes in 828 (35 per cent) vs 1313 (18 per cent): χ^2 = 10007·70, 4DF, $P<0{\cdot}00000$. From the case records: specialists compared to non-specialists performed no axillary treatment in eight (1 per cent) vs 148 (15 per cent); sampled less than four nodes only in 40 (5 per cent) vs 115 (11 per cent); sampled less than four nodes in 12 premenopausal women vs 124 (5 per cent vs 40 per cent of all premenopausal women treated); did not remove any axillary nodes in an axillary sample in six (15 per cent of women with an axillary sample performed) vs 51 (44 per cent). Axillary recurrence was noted in 24 (3 per cent) vs 84 (8 per cent). When examined at 3-year intervals, the specialists have removed four or more nodes in 90 per cent of women with axillary surgery performed, whereas the non-specialists have improved from 66 per cent in the first to 81 per cent in the last interval.
Conclusion: Specialists examine the axilla more frequently, more thoroughly, omit axillary surgery only in very selected cases, and consequently had a recurrence rate almost one third that of non-specialists.

Breast 004

Plasma thrombospondin in early and advanced breast cancer

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Background: Thrombospondin (TSP) has been shown to promote metastasis in animal models by increasing adhesion of cancer cells to endothelial cells. We hypothesized that increased production of TSP by breast cancer would be associated with metastasis.
Method: TSP was measured in the plasma of women with early breast cancer (EBC) ($n=26$), advanced breast cancer (ABC) ($n=29$), women who had undergone surgery for breast cancer with no evidence of recurrent disease ($n=30$) and normal controls ($n=35$). Plasma TSP (pTSP) levels were measured in ng/ml by a radio-immunoassay developed at the University Hospital of South Manchester.
Results: pTSP in women with EBC (median 461 ng/ml, range 172–7750) was elevated when compared to women following surgery (median 230 ng/ml, range 154–547) ($P<0{\cdot}01$) and normal controls (median 180 ng/ml, range 142–356) ($P<0{\cdot}001$). Women with EBC who had nodal metastases ($n=12$) had higher levels of TSP than women who were node negative ($n=14$) ($P<0{\cdot}05$). pTSP in women with high-grade tumours (grades 2 and 3) ($n=16$) was raised when compared to grade 1 tumours ($P<0{\cdot}05$). pTSP levels in women with ABC (median 624 ng/ml, range 209–8820) were higher than in women with no evidence of recurrent disease ($P<0{\cdot}01$) and normal controls ($P<0{\cdot}001$).
Conclusion: Plasma thrombospondin levels are a marker of metastatic disease in early and advanced breast cancer and may be useful in assessing response to chemotherapy.

Breast 005

Tumour bed assessment in ductal carcinoma *in situ*

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Background: Optimal surgical treatment for ductal carcinoma *in situ* (DCIS) involves a wide local excision to ensure tumour clearance. Several methods to assess margins have been described. The aim of this study was to investigate a method of tumour bed assessment by obtaining a shaving of the residual cavity following wide local excision.
Method: Fifty-four patients underwent wide local excision following initial diagnosis of DCIS by stereotactic biopsy or wire localization biopsy. Cavity shavings were obtained after wide local excision and sent separately for histopathology. This tissue was extensively blocked, serially sectioned and extent of residual disease noted. Further surgery was performed based on the extent of disease in the cavity shavings. Adjuvant treatment was administered to 32 patients (59 per cent). Nine patients received adjuvant radiotherapy alone, eight tamoxifen and radiotherapy and 15 tamoxifen alone. Mean follow-up was 35 months (range 4–92 months).
Results: Ten patients (18 per cent) had evidence of residual disease within the cavity shaving. Eight subsequently underwent re-excision or mastectomy. In two patients, no further surgery was performed as only a single focus of DCIS was noted within the tumour bed. The overall local recurrence rate was 7 per cent. All recurrences occurred in the tumour-bed negative group. The original pathology in these patients showed DCIS with high nuclear grade (2 or 3) and associated necrosis histologically and 3 of 4 were clinically palpable.
Conclusion: Obtaining a shaving of the tumour bed is a simple method of assessing residual disease and selective re-excision in tumour-bed positive patients appears to prevent local recurrence. Despite a negative tumour-bed, adverse clinico-pathological features may contribute to local recurrence. These patients may be more appropriately treated by mastectomy.

Breast 006

Axillary dissection is unnecessary in T1 breast cancers with negative sentinel nodes

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Background: The aim of this study was to assess the relative value of lymphoscintigraphy (LSG), blue dye and radioisotope for breast cancer patients having sentinel lymph node biopsy (SLNB) by surgeons inexperienced with the technique and to evaluate the safety of avoiding an axillary dissection when the sentinel lymph node is disease free.
Method: In a prospective study, 110 patients with clinical T1-2N0 breast cancer had SLNB using a combination of lymphoscintigraphy, isosulfan blue dye and technetium sulphur colloid. All of the first 60 patients had a planned axillary dissection while the remainder only had an axillary dissection if the tumour was T2 in size or if the sentinel node was positive.
Results: The sentinel node was successfully identified by LSG in 58 per cent (61/106), by blue dye in 70 per cent (77/110), by isotope in 80 per cent (88/110) and by the combination of blue dye and isotope in 91 per cent (100/110) of all 110 patients ($P<0{\cdot}05$ for combination vs either alone; Fisher's exact test). Success in finding the sentinel node was unrelated to tumour size, type, histological grade or previous surgical biopsy. Failed procedures were no more than frequent in the early (5/55) than in the later experience (5/55). Among the first 60 patients who also had planned axillary dissection, the sentinel node was falsely negative in 2·0 per cent (1/48) of patients with T1 tumours and 17 per cent (2/12) of patients with T2 tumours. The negative predictive value of SLNB for T1 and T2 tumours was 97 per cent and 60 per cent, respectively.
Conclusion: In the first 110 sentinel lymph nodes biopsies, a combination of blue dye and isotope identified the sentinel node more successfully than either method alone. Axillary dissection is unnecessary in T1 breast cancer with a negative sentinel node.

Breast 007

The feasibility, safety, acceptability and cost analysis of early discharge following surgery for breast cancer

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Background: The major determinant of length of postoperative stay following surgery for breast cancer is the magnitude and duration of wound drainage. We wished to determine the feasibility, safety, acceptability and cost effectiveness of early discharge with drains *in situ* using a domicillary nursing service.
Method: The operative details, postoperative drainage, morbidity and analgesic requirements of 37 patients undergoing breast and axillary surgery were prospectively studied. Seventeen were discharged with suction drains *in situ* using the IHNS service. Twenty remained in hospital until drainage was <40 ml/24 h. Selection for early discharge was made using patient preference and geographical considerations. A postal survey was undertaken to assess patient satisfaction in the IHNS group.
Result:

	In patient ($n=20$)	Early discharge ($n=17$)
Age (years)	56·5 (36–75)	59·5 (36–75)
Length of postoperative stay (days)	7 (4–9)	3 (2–8)*
Total drainage (ml)	515 (142–1168)	480 (116–1069)
No. days drains left *in situ*	6 (2–8)	7 (4–11)**
Cost of postoperative care (£)	1500 (750–2000)	775 (300–900)***

Values are medians (ranges); *$P<0{\cdot}0001$, **$P<0{\cdot}05$, ***$P<0{\cdot}0002$, Student's t-test.

The complication rates in the two groups were similar and early discharge was not achieved at the expense of adequate postoperative analgesia.

Eighty-two per cent of the early discharge patients judged the service as excellent, 86 per cent felt they were discharged at the appropriate time and all patients questioned would readily use the service again if it were needed.
Conclusion: Early discharge is feasible, safe, popular and realizes considerable savings. With appropriate domicillary support it could be used in the majority of patients undergoing surgery for breast cancer.

Breast 008

Factors predicting completeness of excision of palpable breast cancers

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Background: This study set out to identify factors available prior to surgery which are associated with completeness of excision of palpable breast cancers treated by breast conserving surgery.
Method: One hundred and sixty-two patients with palpable breast cancers who had attempted breast conserving surgery (wide local excision) where initial mammograms and complete clinical and pathological data were available were reviewed. Analysis was by χ^2 and Fisher's exact tests.
Results: There were 128 (79 per cent) complete excisions and 34 (21 per cent) had involved margins. Factors associated with an incomplete excision were a spiculated mass lesion or area of distortion vs other mammographic features, $P = 0{\cdot}0004$. Twenty-four of 34 incomplete excisions (70 per cent) had this feature. Lesions with spicules extending >50 per cent from the main mass lesion were particularly likely to be incompletely excised, $P = 0{\cdot}0002$. Microcalcification within or outwith a mass lesion and lesions visible on mammography also predicted incomplete excision, $P = 0{\cdot}028$, $P = 0{\cdot}014$, $P = 0{\cdot}023$, respectively. No other features including the experience of the operating surgeon were associated with completeness of excision.
Conclusion: It is possible to predict on the basis of mammographic appearance the majority of cancers that are likely to be incompletely excised by a wide local excision. Patients with these factors should have a very wide excision or should be warned about the possibility of an incomplete excision.

Breast 009

Captopril suppresses tumour-dependent angiogenesis but not physiological angiogenesis on the chick chorioallantoic membrane

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Background: Captopril is a widely used antihypertensive agent that works by inhibiting angiotensin converting enzyme (a zinc dependent carboxypeptidase), it also inhibits matrix metalloproteinases (MMPs) by a similar mechanism and has beneficial effects on several angiogenesis-dependent diseases such as cancer, diabetic retinopathy, arthritis and atherosclerosis. We have used a co-culture of the breast cell line MDA 231 and 'benign' fibroblasts KB 16Fs known to secrete active MMP 2 and 9 to induce angiogenesis on the chick chorioallantoic membrane (CAM) assay.
Method: Using stereoscopic microscopy blood vessels invading a 20 µl collagen gel on the CAM were counted through a 2 × 2 mm nylon mesh over 5 days. Captopril was added to the gels which were capped by a further 10 µl gel containing either no cells, 2×10^{-6} MDA 231s only or co-cultures with 2×10^{-5} KB16Fs. Results are expressed as a percentage of mesh squares containing blood vessels and median angiogenesis scores were compared against captopril-free controls using the Mann–Whitney U-test.
Results: Dose–response curves for captopril on the CAM at concentrations from 10^{-3} to 10^{-6} molar (M) revealed that 10^{-3} M was inhibitory ($P = 0{\cdot}0129$) but that 10^{-5} M ($P = 0{\cdot}0093$) and 10^{-6} M ($P = 0{\cdot}0084$) were stimulatory. MDA 231s and fibroblast co-cultures with 10^{-5} M ($P = 0{\cdot}033$) and 10^{-6} M ($P = 0{\cdot}0433$) captopril were significantly less angiogenic than controls.
Conclusion: When active MMPs are present, captopril reduces angiogenesis significantly at clinically achievable doses but lower doses appeared to enhance angiogenesis when no tumour cells were present. This observation that tumour-dependent angiogenesis is down-regulated and normal embryological angiogenesis is upregulated may suggest a different role for MMPs in both processes.

Vascular 012

Minimally invasive femoropopliteal revascularization: early results of our modified Moll remote superficial femoral endarterectomy

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Background: Minimally invasive vascular surgery should result in a shortened hospital stay, while achieving similar results to conventional surgery. We prospectively assessed a series of patients undergoing our modification of the Moll remote superficial femoral artery (SFA) endarterectomy procedure to assess the viability of this technique.
Method: The indication for Moll remote SFA endarterectomy is disabling claudication in patients who are suitable for above knee femoro-popliteal revasularization. The technique is performed through a single groin incision and does not require any graft material. After initial difficulties with our first two patients, we modified Moll's procedure by inserting a guidewire into the popliteal artery using a 'smart needle' preoperatively. This localizes the distal lumen after endarterectomy preventing atheromatous dissection while inserting the distal stent.
Results: Since February 1997, 21 patients have undergone the modified procedure.

	Technical failures	Successful procedures remaining 1^0 patent	Successful procedures but early occlusion (1 week)
Whole series ($n = 21$)	5	14	2
Learning curve ($n = 10$)	4	4	2
Subsequent cases ($n = 11$)	1	10	0

The mean length of operation was 91 min (range 50–135) and total length of hospital stay was a mean of 1·4 days (range 1–2 days).
Conclusion: Our modification of the Moll remote SFA endarterectomy compares favourably with other minimal access methods of femoropopliteal revascularization in terms of technical success and patency, and is attractive in terms of short operating time and hospital stay. We believe that this technique may become the procedure of choice for above knee femoropopliteal revascularization.

Vascular 013

Transduction of haemodynamic forces in vein graft endothelium by ion channels

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Background: Arterial flow alters the adhesive and thrombotic surface of saphenous vein endothelium by inducing rapid upregulation of ICAM-1 and nitric oxide synthase (eNOS) and downregulation in thrombomodulin (TM) expression. The aim of this study was to investigate whether these effects are dependent on the following ion channels: stretch activated cation (SAC), calcium and ATP-sensitive potassium (K^+_{Ca2+} and K^+_{ATP}), and L-type calcium (Ca^{2+}) channels.
Method: Saphenous vein segments were perfused with oxygenated Krebs solution, mean pressure 100 mmHg, 80 cpm, shear stress 0·3 ± 0·1 N/m^2, in an *in vitro* bypass circuit for 90 min. Vein and endothelial viability were confirmed by ATP assay and CD31 staining. ICAM-1, eNOS and TM were assessed by immunostaining. Protein concentration was estimated by quantitative image analysis expressing staining as a percentage of control protein CD31. Gadolinium (Gd^{3+}, 10 μM), tetraethyl ammonium (TEA), 3 mM, glibenclamide (glib), 5 μM, and nifedipine (nif), 20 μM, were added to the perfusate in separate experiments to block SAC, K^+_{Ca2+}, K^+_{ATP}, and Ca^{2+} channels, respectively. Controls were freshly excised vein (basal) and vein exposed to venous flow (20 mmHg, 0·02 ± 0·01 N/m^2).
Results: These are given as percentage of CD31 area, mean ± standard error of six experiments. $^*P \leq 0{\cdot}01$ compared to arterial flow 90 min. No changes were observed after venous flow for 90 min.

Flow conditions	Channel blocked	ICAM-1	TM	eNOS
Basal	—	21·4 ± 1·4	68·4 ± 6·0	50·0 ± 5·6
Arterial flow (90 min)	None	44·6 ± 2·0	32·9 ± 3·0	70·1 ± 5·0
Arterial & Gd^{3+} (90 min)	SAC	21·2 ± 2·4*	75·6 ± 3·5*	84·5 ± 6·0
Arterial & nifedipine (90 min)	CA^{2+}	38·0 ± 2·3	78·0 ± 4·0*	55·8 ± 3·1*
Arterial & glibenclamide (90 min)	K^+_{ATP}	21·7 ± 3·5*	50·2 ± 6·0	66·1 ± 6·0
Arterial & TEA (90 min)	K^+_{Ca2+}	20·0 ± 1·0*	43·4 ± 4·0	47·0 ± 3·0*

Conclusion: Ion channels regulating the flux of K^+ and Ca^{2+} mediate mechanotransduction in saphenous vein endothelium, e.g. blocking Ca^{2+} entry prevents upregulation of eNOS whilst Gd^{3+} prevents the unwanted changes in ICAM-1 and TM. Selective ion channel blockade of ICAM-1 upregulation and TM downregulation may lead to a more favourable outcome to vein bypass.

Vascular 014

Lipid abnormalities in new referrals to vascular outpatients

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Background: The aim of this study was to evaluate the benefits of a policy of performing screening blood tests in new patients with arterial disease referred to the vascular outpatients department.
Method: Clinical audit over a 12-month period of all new referrals with arterial disease to the vascular outpatients department at the Leicester General Hospital.
Results: Two hundred and seventy-two patients had at least one blood test performed at their outpatient visit. All of these patients had a full blood count performed, of which 21 results were abnormal. Further investigations of patients with abnormal results revealed one case of bladder cancer, one case of leukaemia and one patient with polycythaemia. Urea and electrolytes were measured in 269 patients (99 per cent). Of these 26 (10 per cent) were expectedly abnormal in patients with known renal impairment. A further 27 patients (10 per cent) were identified as having some degree of unrecognized renal impairment. Serum non-fasting glucose was measured in 252 patients (93 per cent). There were 11 unexpectedly raised results but further investigation of these patients diagnosed only one as diabetic. Serum cholesterol was measured in 201 patients (74 per cent). One hundred and thirty-two patients (66 per cent) had an abnormally raised serum cholesterol level. Of these only 12 patients (6 per cent) were known to have hyperlipidaemia.
Conclusion: Screening new patients with arterial disease in vascular outpatients identifies significant abnormalities, in particular renal impairment and hyperlipidaemia. Correction of these abnormalities may reduce the morbidity associated with contrast-induced nephrotoxic acute renal failure, and also contribute to secondary prevention of vascular events associated with raised lipids.

Vascular 015

Trends in lower limb amputee management: 3-year results from a national survey

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Background: This study had two aims: 1) to establish a system of data collection, audit and analysis for all lower limb amputees in Scotland, and 2) to create a demographic profile of the amputee population from which regional comparisons can be made.
Method: The Scottish Physiotherapy Amputee Research Group (SPARG), in collaboration with the Scottish Vascular Audit Group (SVAG) has developed a discharge summary form for all lower limb amputees. This was tested and introduced nationally in 1992. There are 24 designated SPARG hospitals spread throughout Scotland. Discharge forms are initiated at the amputating hospital and follow the patient should they be transferred. Ten hospitals enter data directly on to computer by means of SPARG software; others return forms to the SPARG co-ordinator. Patient numbers are checked with the Information and Statistics Division at the Scottish Office. Statistical analysis is carried out on three rehabilitation milestones: 1) number of days from amputation to casting (for prosthesis), 2) number of days from casting to delivery (of prosthesis, and 3) number of days from amputation to discharge. Analysis of compression therapy (CT) and early walking aid (EWA) use is also conducted.
Results: The amputee population is very stable. There are approximately 700 primary major amputations each year. Some 90 per cent of patients have peripheral vascular disease with 35 per cent reported as diabetic at the time of surgery. More than 60 per cent of amputations are at the transtibial (TT) and 30 per cent at the transfemoral (TF) level. Some 75 per cent of TT and less than 40 per cent TF amputees receive a prosthesis. Inpatient mortality is 14 per cent nationally (range 4–38 per cent). Stump infection occurs in 18 per cent of patients. Milestone data are broadly similar year to year although considerable differences are noted between centres. For TT amputees, crepe bandage as a CT confers no significant improvement over no compression bandage for 'days to casting' milestone, whereas use of an Elset 's' shrinker sock, or both, results in a reduced time ($P<0{\cdot}01$). Use of EWAs produces the same effect. Patients with a plaster cast as a compression dressing have a reduction in 'days to casting' compared to those using other CT ($P<0{\cdot}01$). 'Casting to delivery' times vary greatly. The figures for 'amputation to discharge' show a similar variation with a national mean of about 60 days for TT and 70 days for TF amputees (figures for patients fitted with a prosthesis). The one centre where a rigid postoperative dressing is routinely applied to TT amputees has a consistent and significant reduction in 'days to casting' ($P<0{\cdot}01$) and 'days to discharge' ($P<0{\cdot}05$) compared with the national average.
Conclusion: A national demographic profile has been established from which local comparisons, national and regional audit can be carried out. The apparent advantages to patients offered by the application of a postoperative rigid plaster-of-Paris dressing warrant further investigation.

Vascular 016

Ilio-popliteal grafts: a useful option for limb salvage

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Background: The aim of this study was to assess the durability of bypass grafts using the iliac artery as the inflow vessel for patients with multilevel atherosclerotic occlusive disease.
Methods: Forty-six patients underwent bypass grafts from the iliac artery to the popliteal or tibial arteries. Surgery was performed for critical ischaemia in 43 cases and for severe claudication in three. Six patients had previous iliac angioplasty and eight had previous vascular surgical reconstructions. Two patients had had a contralateral major limb amputation. All patients had multilevel occlusive disease on arteriography. The profunda femoris artery was severely diseased in 18 patients (39 per cent). In a further 17 (37 per cent) the common femoral artery was also unreconstructable. Fifteen patients had three vessel run-off, 22 had two vessel run-off and nine patients had single vessel run-off. A retroperitoneal approach to the iliac artery was used in 31 cases, and extended longitudinal groin incisions in the others. All grafts were tunnelled extra-anatomically. The external iliac artery was used as the donor vessel in 36 patients and the common iliac artery in ten. Thirty-one grafts were inserted to the above knee popliteal artery, 13 to the below knee popliteal, and two to the posterior tibial artery. Externally reinforced polytetrafluoroethylene grafts were used in 40 cases and reversed long saphenous vein in six.
Results: Over a median follow-up of 22 (range 1–63) months, the observed median duration of graft patency was 19 (range 1–53) months for the above knee grafts, and 17 (range 1·5–63) months for below knee grafts. By life-table analysis, cumulative patency rates at 12 and 24 months were 73 per cent and 73 per cent, respectively for the above knee grafts, and 80 per cent and 67 per cent, respectively for the below knee grafts. Graft occlusion occurred in 12 patients (26 per cent), eight of whom required a major limb amputation (seven above-knee, one below-knee). One patient developed a graft infection; the graft was removed and he subsequently had an above knee amputation.
Conclusion: In patients with critical limb ischaemia due to complex multi-level atherosclerotic disease, the ilio-popliteal graft is a useful surgical option for limb salvage.

Vascular 017

Is formal quality-of-life analysis necessary in patients with lower limb ischaemia?

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Background: Quality of life (QoL) is an increasingly popular outcome measure in vascular surgery. This prospective study aims to assess the correlation between the clinical indicators of lower limb ischaemia (LLI) and QoL.
Method: Over 2 years, 281 patients, 178 men and 103 women, median age 67 (range 40–87 years), underwent 1264 assessments. Patient-reported walking distance (PRWD), intermittent claudication distance (ICD), maximum walking distance (MWD) on a treadmill testing, ankle:brachial pressure indices at rest (ABPIR) and post-treadmill testing (ABPI PT) were recorded at each assessment if possible. Patients completed the EuroQol which derives three global QoL scores using categorical (Cat) data, time trade-off (TTO) data and a visual analogue scale (VAS).
Results:

		Spearman rank correlation coefficient		
Clinical indicators of lower limb ischaemia	*n*	EuroQol Cat	EuroQol VAS	EuroQol TTO
PRWD	1264	–0·44	0·53	0·62
ABPI R	1246	–0·27	0·24	0·35
ABPI PE	1067	–0·30	0·2	0·33
ICD	872	–0·25	0·29	0·34
MWD	1157	–0·36	0·47	0·57

Conclusion: Overall the correlation between QoL and clinical indicators of LLI is disappointingly low as reflected by the low correlation coefficients. This suggests QoL variations cannot be assumed to mirror variations in the clinical indicators of LLI, and independent QoL assessment is required.

Vascular 018

Peripheral thrombolysis and the fate of the claudicant

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Background: The aim of this study was to determine the outcome of patients who presented with sudden onset of incapacitating claudication and were treated with peripheral arterial thrombolysis within 2 weeks of the onset of symptoms.
Method: Some 108 patients (67 men, median age 69; range 29–94 years) were treated with intra-arterial tissue plasminogen activator thrombolysis at 14 hospitals between June 1992 and June 1997. The median duration of symptoms was 72 h (range 2 h to 2 weeks) and there were 52 graft occlusions (28 polytetrafluoroethylene, 14 vein, three Dacron, three composite, three unknown).
Results: Complete thrombolysis was achieved in 54 patients, clinically useful lysis in 25, lysis but no run-off in 19 and lysis failed in 10. Angioplasty of an underlying lesion was carried out in 39 patients; 10 had a thrombo-embolectomy, seven had graft reconstruction, one had an endarterectomy and 44 had no secondary intervention. There were 15 deaths, most from cardiovascular cause, although three, including two strokes, may have been complications of treatment. The median age of these patients was 73 years (range 63–90 years) compared with 68 years (range 29–94, $P = 0{\cdot}005$, Mann–Whitney) for the survivors. Eight patients had a major amputation either because there was no viable calf vessel after thrombolysis or after a failure of secondary intervention. There were six major bleeds, five from the arterial puncture site.
Conclusion: These results show a poor outcome in 23 per cent of patients treated for symptoms of claudication. This may be because the patients were progressing towards limb-threatening ischaemia at the time of treatment, thrombolysis caused calf vessel occlusion or because the lack of a definition for acute limb ischaemia has made classification of these patients difficult.

Vascular 019

An outcome audit of 99 consecutive thoracoscopic sympathectomies

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Background: Thoracoscopic sympathectomy (TS) is an effective treatment for palmar hyperhidrosis but its role in axillary hyperhidrosis, digital vascular disease and causalgia is uncertain. We have reviewed our total experience of TS.
Method: All records of patients undergoing TS between January 1992 and July 1997 were analysed. Clinical indications, immediate and late outcomes and complications were recorded. Follow-up was performed for all patients by completion of a postal or telephone questionnaire.
Results: Ninety-nine thoracoscopic sympathectomies were performed in 60 patients. The indications were palmar hyperhidrosis (80), axillary hyperhidrosis (11), digital ischaemia (6), Raynaud's disease (1) and causalgia (1). Thirty-six females and 18 males (median age 28·8 years, range 15–48 years) underwent surgery for hyperhidrosis. All patients treated for palmar hyperhidrosis were initially cured. Surgery for axillary hyperhidrosis was technically successful in all but one case. Although axillary anhidrosis was not achieved in any patient, all who had successful surgery were satisfied that their symptoms were considerably ameliorated. Patients were discharged one day postoperatively except for one who required a chest drain. Compensatory sweating developed in 24 patients (21 trunkal, 6 gustatory, 5 perineal, 5 facial, 5 plantar and 3 axillary). Compensatory truncal sweating was most severe after bilateral sympathectomy. Complications occurred in eight patients (three pleuritic chest pain, two intercostobrachial neuralgia, one intercostal vessel haemorrhage, one arm stiffness and one spontaneously resolving pneumothorax). There were no eye signs of Horner's syndrome. All complications resolved without further intervention. Nine patients reported some return of palmar sweating but they considered this a better outcome than anhidrosis. Three patients developed recurrent palmar hyperhidrosis at 6, 15 and 21 months postoperatively. The patient with the 6-month recurrence underwent a second thoracoscopic sympathectomy without further recurrence at 2 years. Two patients treated for digital ischaemia have since died. The remaining patients did not improve following TS.
Conclusion: Thoracoscopic sympathectomy was initially successful in all cases of palmar hyperhidrosis and 91 per cent of hyperhidrotic axillae. The main adverse effect was compensatory sweating which was more common after bilateral sympathectomy. The recurrence rate for palmar hyperhidrosis was 5·4 per cent, but repeat sympathectomy was successful in the one case in which it was attempted. Other recently suggested therapies for palmar hyperhidrosis will need to match these cure rates.

Vascular 020

Duplex scanning is unnecessary in all patients with primary, non-recurrent varicose veins

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Background: Duplex scanning of all patients undergoing varicose vein surgery is controversial. The aims of this study were: (i) to compare the accuracy of hand-held Doppler (HHD) assessment with duplex scanning in patients with varicose veins; (ii) to assess the benefit of tourniquet testing; and (iii) to identify patients who may benefit from a policy of selective duplex scanning.
Method: Venous reflux was assessed using HHD with an 8 MHz probe immediately followed by duplex scanning in 72 patients with primary, previously untreated varicose veins (108 limbs).
Results: HHD accurately assessed saphenofemoral junction reflux (sensitivity 0·93, specificity 0·91, positive predictive value 0·96, negative predictive value 0·85) and long saphenous vein reflux (sensitivity 0·95, specificity 0·68, positive predictive value 0·91, negative predictive value 0·80). HHD assessment of saphenopopliteal junction (SPJ) reflux was less accurate (sensitivity 0·82, specificity 0·80, positive predictive value 0·43, negative predictive value 0·96), although the high negative predictive value indicated that absent SPJ reflux is assessed accurately using HHD. Tourniquet testing was not helpful.
Conclusion: Selective duplex scanning of limbs with suspected SPJ reflux, no identifiable site of reflux or posterior thigh perforator reflux on HHD (39 per cent of limbs), would have resulted in the appropriate surgical procedure being performed in 102 (94 per cent) limbs, excessive surgery in five (5 per cent) limbs and inadequate surgery in only one (1 per cent) limb. The use of selective criteria for duplex scanning would reduce the workload of the vascular laboratory without compromising patient care.

Vascular 021

Can we stop recurrent varicose veins? A prospective observational study

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Background: Accurate preoperative diagnosis and adequate surgery undoubtedly help to reduce but not eliminate recurrent varicose veins. Other factors are therefore also important. The aim of this study was to assess the influence of disease progression and accuracy of varicose vein surgery on duplex-derived evidence of incompetent veins.
Method: Sixty legs in 45 patients (median age 50, range 27–75 years) undergoing varicose vein surgery were assessed and followed-up in a prospective observational study. All patients had duplex ultrasound imaging of their leg at three time points: preoperatively, at 6 weeks postoperatively, and at 1 year postoperatively. Venous mapping of sites of incompetence was performed systematically for comparison at each time point.
Results: Surgery successfully abolished all sites of pre-existing reflux. The postoperative duplex scan at 6 weeks revealed that new sites of reflux, not identified preoperatively, had developed in 12 limbs. At 1 year the reflux seen in six of these patients had disappeared entirely. New reflux, not present at the 6 week postoperative scan, was demonstrated in a further five patients at 1 year.
Conclusion: Varicose vein surgery can alter the haemodynamics of venous return. This may contribute to new sites of venous incompetence in the early postoperative period; these may disappear spontaneously.

Vascular 022

An audit of current management of varicose veins

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Background: This study aimed to evaluate current management of varicose veins by vascular surgeons.
Method: A questionnaire was sent to all 427 members of the Vascular Surgical Society.
Results: The response rate was 65 per cent, of whom 77 per cent were general surgeons with a vascular interest (Group A), 21 per cent were vascular only (Group B), and 2 per cent were non-vascular (Group C). Seventy-three per cent of respondents see varicose vein patients in a vascular or a dedicated venous clinic. The median (range) number of patients seen per week is five (0–78) and the waiting time to be seen is 12 (1–150) weeks. Three (0–12) varicose vein operations per week are performed of which 10 per cent (0–50 per cent) are for recurrence and 50 per cent (0–96 per cent) are day cases. Sixty-five per cent of surgeons use hand-held Doppler routinely in the assessment of varicose veins and 85 per cent use duplex scanning as their first line other investigation. Eighty-one per cent and 67 per cent perform synchronous bilateral surgery for long and short saphenous vein varicose veins, respectively. Day-case surgery is performed for primary long saphenous vein (LSV) varicose veins by 86 per cent, for unilateral recurrence by 51 per cent, and for primary bilateral varicose veins by 32 per cent. For primary LSV varicose veins 90 per cent perform saphenofemoral disconnection, 82 per cent stripping to the knee, 2 per cent stripping to the ankle and 95 per cent multiple avulsions. For recurrence associated with groin reflux 94 per cent perform groin re-exploration and 75 per cent strip a residual LSV. For recurrence associated with reflux in the popliteal fossa 91 per cent perform re-exploration of the popliteal fossa and 27 per cent strip a residual short saphenous vein. Thirty-five per cent do not stop any hormone therapy prior to surgery. Surgical practice was similar in Groups A and B. Sixty-eight per cent of respondents perform sclerotherapy for varicose veins on the NHS, predominantly for isolated small varicose veins and missed varicose veins following surgery.
Conclusion: The management of varicose veins by most vascular surgeons is similar. There remains a variety of practice in relation to hormone therapy and varicose vein surgery.

Vascular 023

An evaluation of pin stripping vs conventional stripping in the treatment of primary varicose veins: pilot study

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Background: Stripping of the long saphenous vein (LSV) can be considered vital in the surgical treatment of primary varicose veins when valvular incompetence is present. Ensuring the high tie and stripping is accurate and effective can also prevent recurrence. Removal of the LSV can be achieved in a variety of different ways. This study is a comparison of two such methods. This study aimed to examine the efficacy of perforate invagination (PIN) stripping in comparison to conventional stripping in a prospective randomized trial.
Method: Eighty patients were recruited to undergo stripping of the LSV as indicated by their clinical need. They were randomized to PIN or conventional stripping with all other operative techniques remaining constant. Postoperatively all patients were followed-up for 1 week.

Results:

	Time to strip veins (min)	% vein stripped	Size of exit site (cm)	Area of bruising (cm^2)
Median (IQR)				
C (range)	5·57 (4·46–8·17)	89·64 (67·03–100)	0·55 (0·5–0·7)	91·5 (68–153)
P (range)	5·30 (4·41–9·38)	85·71 (52·48–100)	0·4 (0·35–0·5)	84 (54–167)
P level	0·736	0·496	0·0049	0·749

C = conventional; P = PIN.

Conclusion: There was no statistically significant difference in terms of speed and efficacy of use and morbidity from postoperative bruising between the PIN and conventional stripper. The PIN resulted in smaller exit wound which was statistically significant.

Vascular 024

Thromboembolism after varicose vein surgery

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Background: There are no clear guidelines for heparin prophylaxis in varicose vein surgery but there is a risk of litigation from a patient on the oral contraceptive pill (OCP) or hormone replacement therapy (HRT) who suffers a thromboembolic complication. The risk of thromboembolism is too low for a controlled trial to solve the question so practice varies according to individual prejudice.
Method: A database of 1185 patients (830 women: 355 men, mean age 49 years, range 16–83) who had varicose vein surgery over 12-years was reviewed.
Results: Deep vein thrombosis (DVT) occurred in six (5 men: 1 woman, mean age 59 years, range 48–66). One man had a non-fatal pulmonary embolism; one had a history of previous DVT; one suffered an axillary vein thrombosis. Male risk of DVT was 5/355 (1·4 per cent). The one woman with DVT was 66 years of age and not on HRT. Female risk of DVT was 1/830 (0·12 per cent). The sex difference was significant by χ^2 analysis ($P<0·02$). A subset of the last 181 women showed 13/89 (15 per cent) 'eligible' 20–49 year olds on the OCP, and 17/103 (17 per cent) 'eligible' 40–69 year olds on HRT. Overall no women on OCP/HRT suffered from thromboembolism, but only 16 per cent of this subset (30/188) were exposed to the risk.
Conclusion: We regard previous DVT as the highest risk factor and recommend Enoxaparin 40 mg subcutaneously for 8 days. Patients on OCP/HRT should receive heparin 5000u subcutaneously while in hospital (often only 1–2 doses), but the present evidence suggests male sex is a greater risk factor so we conclude that it may be simpler to give heparin to all patients, hoping that 1–2 doses will have an effect.

Vascular 025

A specialized community leg ulcer service: the Gloucestershire experience

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Background: This study evaluates healing and recurrence of chronic leg ulcers in East and West Gloucestershire before and after establishment of a specialized vascular-led community-based service in East Gloucestershire.
Method: In East Gloucestershire, outcome of a random sample of chronic leg ulcers ($n=100$) from 3 months before clinics was compared to that of consecutive limbs ($n=200$) subsequently managed in specialized clinics. West Gloucestershire was the control in this study with random samples of chronic leg ulcers ($n=100$) being compared from 3-month intervals before and after clinics had been established in neighbouring East Gloucestershire.
Results: The 24-week healing and 1-year recurrence rates of limbs with completed 12-month follow-up are summarized below:

	Before		After	
	East	West	East Clinics	West
Ulcerated limbs	100	100	200	100
Validated chronic leg ulcers	97	97	200	93
24-week healing	29 (30%)*	21 (22%)	135 (68%)*	26 (28%)
1-year recurrence	37/79 (47%)*	26/59 (44%)	26/114 (23%)*	20/58 (35%)

*$P<0·01$ (χ^2-test).

Conclusion: Chronically ulcerated limbs assessed, managed and followed in a specialized community service had improved in both healing and recurrence after 1 year.

Vascular 026

Calman, venous surgery and the vascular trainee

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Background: Venous surgical training has traditionally been the 'Cinderella' of vascular surgery. With the advent of Calman training and Vascular Surgical Society recommendations, we have audited the venous surgical experience of Vascular Trainees.
Methods: Questionnaires were sent to 90 vascular surgical trainees achieving a 77 per cent response rate ($n=69$).
Results: Twenty-eight (41 per cent) trainees had spent >12 months on a pure vascular firm, compared to 37 (54 per cent) on a general/vascular firm. While the majority had been trained in saphenofemoral junction ligation (91 per cent) and saphenopopliteal junction ligation (87 per cent), only 59 per cent used preoperative duplex and only 14·5 per cent preoperative venography. The use of newer techniques such as perforate invagination (PIN) stripping (42 per cent), Oesch hooks (39 per cent), or Muller hooks (22 per cent), were all comparatively low. Nineteen trainees (27·5 per cent) had not received training in the use of any hook devices in varicose vein surgery. Recurrent varicose vein surgery revealed further deficits. Thirty per cent of trainees had not received specific training in the lateral approach to a persistent saphenofemoral junction. This was even more marked for the superior (67 per cent) and medical approaches (81 per cent). Deep venous surgical training was sparse. The majority of trainees (75 per cent) had not received any training. Indeed only one operation was actually performed by a trainee. No formal training in sclerotherapy was received by 21 (30 per cent) of trainees, and 74 per cent ($n=51$) had not been trained in the use of microsclerotherapy techniques. Separating the trainees into those with greater or less than 12 months' experience on both general vascular and pure vascular firms reduced, but did not eliminate, these deficits.
Conclusion: Current training schedules do not cover the field of venous surgery adequately. Vascular specialists should aim for a broader venous surgical training, tailored to the trainees' experience on entry to their firm.

Vascular 027

The natural history of infrainguinal vein grafts performed for popliteal aneurysms

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Background: The treatment of choice for popliteal aneurysms is infrainguinal venous bypass grafting, however, no long-term follow-up studies of these grafts have previously been described. The aim of this study was

to establish the natural history of infrainguinal vein grafts that had been performed for popliteal aneurysms.
Method: Between 1988 and 1997, 351 infraguinal vein grafts were performed, 27 of these were for a popliteal aneurysm of 3 cm or more in diameter. Standard operative technique was Hunterian ligation of the aneurysm and bypass grafting using autologous vein. All grafts were included in a vein graft surveillance programme and data were collected from a surveillance database and case-note review.
Results: There was no difference in the sex, age and risk factor distribution between patients receiving vein grafts for popliteal aneurysm or occlusive disease. In patients grafted for popliteal aneurysm, the median follow up was 41 months (1–98 months). Six (22 per cent) grafts developed a significant stenosis (peak velocity ratio >2·5) within the first 6 months of follow-up; after this no further *de novo* or recurrent vein graft stenoses occurred. This group of patients had an overall lower incidence of vein graft stenosis than grafts performed for occlusive disease ($P<0{\cdot}038$). Subsequently, 12/27 (44 per cent) of the vein grafts developed spontaneous true aneurysms after a median of 30 months (7–84 months). Four of these reached 3 cm in diameter and had elective revisional surgery. The incidence of true aneurysm formation in this group was significantly higher than vein grafts for occlusive disease ($\chi^2 = 97{\cdot}3$, $P<0{\cdot}001$ with Yates continuity correction). Five-year cumulative primary, primary assisted and secondary patency rates were 58 per cent, 76 per cent and 82 per cent, respectively which are all higher than the rates for vein grafts for occlusive disease, 23 per cent, 52 per cent and 60 per cent, respectively (log rank test, $P = 0{\cdot}0128$, 0·058 and 0·0063).
Conclusion: Vein grafts performed for popliteal aneurysms had a lower incidence of vein graft stenosis but a significantly higher rate of spontaneous true aneurysm formation. Vein grafts performed on these patients should therefore be monitored in a surveillance programme indefinitely.

Vascular 028

Vein graft surveillance can stop after 1 year, but limb surveillance is for life

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Background: It has been suggested that vein graft surveillance can be stopped after 1 year due to the low incidence of vein graft stenosis after this time. This approach may have important cost saving implications. Vein grafts that develop stenoses are at greater risk of developing further stenotic lesions and need to be monitored closely. The aim of this study was to establish whether surveillance could be stopped after 1 year in infrainguinal vein grafts that had not developed *de novo* arterial or vein graft lesions within that time period.
Method: Data were collected prospectively on 326 patients who had undergone 351 infrainguinal venous bypass grafts between 1988 and 1997. Vein graft surveillance occurred at 1, 3, 6, 9, 12 months and at 6-month intervals thereafter. Duplex imaging examined the vein graft and arterial inflow/run-off vessels in each limb. A significant vein graft stenosis was diagnosed when a peak systolic velocity ratio was greater than 2. Grafts that had not developed a significant stenosis during the first year of surveillance were investigated further to establish the incidence and risk of developing subsequent *de novo* stenotic lesions.
Results: One year cumulative limb salvage, patient survival, primary, primary assisted and secondary patencies were 81 per cent, 77 per cent, 44 per cent, 67 per cent and 81 per cent, respectively. One hundred and four (29·6 per cent) grafts developed a significant primary vein graft stenosis, 95 (91 per cent) of which occurred within 12 months. After 1 year, the average risk of developing a significant graft stenosis was 3 per cent per year. Sixty-nine grafted limbs developed arterial inflow/run-off stenoses that required intervention, but only 37 (54 per cent) occurred within the first year, after which, the average risk was 9 per cent per year. After 1 year, only 78 grafts/limbs could be identified that had not developed *de novo* vein graft/arterial inflow or run-off stenoses. Subsequently 17 (21·8 per cent) of these grafts went on to develop primary vein graft and/or arterial stenotic lesions that required intervention. The overall average risk was 9·5 per cent per year of developing a *de novo* vein graft or arterial stenosis in a limb.
Conclusion: The risk of developing a stenosis in a vein graft drops considerably after 1 year. However, *de novo* arterial lesions, that may threaten graft patency, occur at a rate of 9 per cent per year. Vein graft surveillance could stop at 1 year but the limb is still at risk of developing potentially graft-threatening arterial stenoses and therefore limbs that have undergone infrainguinal vein bypass grafting must continue to be monitored in a surveillance programme for life.

Vascular 029

Plasma homocysteine is an independent risk factor for vein graft stenosis

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Background: This study investigated the association between hyperhomocysteinaemia and the development of stenosis in infrainguinal vein bypass grafts.
Method: Sixty-one patients, 62 limbs (44 men) with median age 72 years (range 35–95) undergoing femorodistal vein bypass were recruited. Fifty-eight per cent had surgery for critical limb ischaemia (CLI), 30 per cent for intermittent claudication (IC), 8 per cent for correction of asymptomatic vein graft stenosis (VGS), and 4 per cent for acute limb ischaemia (ALI). All patients underwent a 1-year graft surveillance programme. Fasting plasma total homocysteine (THC) levels together with other putative markers for development of vein graft stenosis (fibrinogen, lipid profile, and cotinine) were measured. Serum B12 and red cell folate (RCF) were measured as factors which mainly affect THC levels.
Results: After 12 months, 42 grafts were classified non-stenosed and 20 stenosed. Median THC levels were 9·5 µmol/ml (range 5·4–32·0) in the no-stenosis group and 14·4 µmol/ml (9·6–32·0) in the stenosis group ($P<0{\cdot}0001$, Mann–Whitney U-test). (Reference range for THC was 5·0–15·0 µmol/ml.) Median plasma fibrinogen levels were 2·85 mg/ml (1·8–6·6) in the no-stenosis group and 3·72 mg/ml (2·37–8·0) in the stenosis group ($P<0{\cdot}003$ Mann–Whitney U-test). Median RCF levels in the no-stenosis group were 284·0 µg/ml (118·5–649) and 197·5 µg/ml (96·0–591·0) in the stenosis group ($P<0{\cdot}04$ Mann–Whitney U-test). In this study serum B12, lipid profile and cotinine were not significantly associated with stenosis on univariate analysis.
Conclusion: Raised levels of THC are strongly associated with graft stenosis. Reduction of plasma THC by folate supplementation may prevent development of stenosis in at risk patients.

Vascular 030

Is acute normovolaemic haemodilution a useful adjunct to blood conservation in peripheral vascular surgery?

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Background: This study aimed to establish the extent to which acute normovolaemic haemodilution (ANH) can be applied to lower extremity peripheral vascular surgery as a blood conservation method to minimize patient exposure to homologous blood transfusion (HBT).
Method: Forty patients, 26 men and 14 women, with a median age of 68 years, undergoing elective femorodistal bypass for chronic critical ischaemia were recruited prospectively with an intention to avoid perioperative HBT. Recommended exclusion criteria were applied and transfusions were given in cases of large volume blood loss and symptomatic anaemia.
Results: Fifteen (37 per cent) of the patients were excluded preoperatively because of poor left ventricular function, anaemia or renal impairment and a further six because of a fall in haematocrit to less than 35 per cent due to colloid/crystalloid requirements before surgery. Median blood

loss was 1150 ml and median blood collected 1040 ml suggesting reasonable utility on the remaining patients in preventing HBT. Eleven patients, however, lost less than 650 ml and would have avoided HBT in any case. Two patients lost over 2·5 L and required intraoperative transfusion. Two of the remaining six patients suitable for ANH and with moderate blood loss (950–1400 ml) required transfusion in the immediate postoperative period due to symptomatic anaemia. Only four patients avoided exposure to HBT.
Conclusion: Preoperative co-morbidity and the variability of blood loss during peripheral vascular surgery combine to make the complex process of ANH of very modest value to the patient undergoing peripheral vascular surgery.

Vascular 031

A strategy for vascular services: testing the hypothesis

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Background: The delivery of vascular services has been criticized and reorganization based upon a suggested population of 600 000, with the two underlying principles being that patients with vascular problems should be treated by surgeons with a vascular practice and that the surgeon should have a 1:4 rota. The aim of the study was to test the hypothesis in three disparate regions.
Method: North West Thames, Wessex and East Anglia were assessed for vascular operations/10 000 population and hospital activity for 1994/95 (Hospital Episode Statistics [HES]). Activity statistics were validated against unit audit in one hospital for each region. A surgeon from each hospital replied to a questionnaire regarding resources.
Results: There was little variation in the operations/10 000 between the three regions (range 4·55–4·99). All these regions had four units providing a service for more than their local population. In one region all these units were also performing more than 200 operations per year and more than 20 carotid endarterectomies per year, but in the other two regions only two units met these criteria. These four units (most of which are in district hospitals) could, between them, provide a service for 2 400 000, leaving the option for smaller units (based upon 300 000) to provide the service for geographically inaccessible areas. The HES activity had >90 per cent concordance with local audit in all regions and inadequate facilities were not related to low vascular throughput (questionnaire response rate >70 per cent in all regions). Four hospitals in one region and five hospitals in two regions performed <50 vascular operations per year and it might be advantageous to transfer these patients to another hospital.
Conclusion: With co-operation, a strategy based upon a smaller number of units providing full vascular cover throughout the year could be effective in all three regions studied.

UGI 010

Cost-effectiveness and quality of life in individuals undergoing treatment for oesophageal carcinoma

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Background: This study aimed to assess the relationship between clinical outcome, quality of life (QoL) and cost for the treatment modalities most commonly employed in the management of oesophageal carcinoma.

Method: Individuals diagnosed with oesophageal carcinoma in 1993 and managed in Newcastle upon Tyne were identified from Hospital Episode Statistics (HES) and the Northern Cancer Registry. Post-treatment interventions and outcome over a 3-year follow-up period were recorded. A cost-analysis profile was derived prospectively from a cohort of patients diagnosed over a 6-month period in 1996–97 who also underwent QoL asessment at monthly intervals over a 3-month period using the EORTC QLQ-C30 and OES24 disease-specific modules. Costs were calculated for radiotherapy (DXT), endoscopic and surgical procedures (accounting for staff and equipment costs in each case) as well as the cost of outpatient, in-patient and ITU attendance. Cost, QoL and survival were compared between treatment groups using the Mann–Whitney U and log rank tests.

Results: One hundred and thirty-nine individuals were identified retrospectively for the cost analysis and a further 51 recruited prospectively to assess quality of life. Survival was significantly better in patients treated by resection ($n=31$; median survival = 20 months) than for those receiving palliative treatment options ($n=108$; median survival = 6 months) ($P<0\cdot0001$). QoL measurements suggested significant improvement in reported dysphagia at 2 and 3 months post-treatment only for individuals who underwent resection although even this was at the expense of significant impairment of reported physical function and global health/QoL. Median cost was significantly greater in individuals who underwent resection (£8070) than for patients subjected to a palliative strategy (DXT = £4720, brachytherapy = £1790, laser = £3540, intubation = £2450, no treatment = £1390) ($P<0\cdot01$). When considering the median cost per month of life intubation and no intervention proved to be the most costly of the palliative options (£1125 and £971, respectively) compared with DXT at £693, brachytherapy at £364 and laser at £342. Resection (£457 per month) compared favourably for cost per month with these palliative options.

Conclusion: Surgical resection for oesophageal carcinoma results in the best survival and improvement in reported dysphagia. In view of the longer survival, costs are inherently greater in individuals undergoing resection; allowing for time, resection is at least as cost-effective as any other treatment modality.

UGI 011

Adjunctive chemoradiotherapy in oesophageal carcinoma: no increase in postoperative morbidity or mortality

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Background: The oncological benefit of preoperative chemo- and radiotherapy followed by surgery in oesophageal cancer has been established, with improved disease-free and overall survival reported. Assurances that this benefit is not at the cost of increased perioperative wound and septic complications as a result of the neoadjuvant therapies is required.

Method: We performed a detailed analysis of morbidity and mortality associated with these factors in randomized clinical trials of patients with oesophageal cancer receiving either neoadjuvant chemo- and radiotherapy prior to surgery or surgery alone. All complications that may be influenced by abnormal wound healing or immune function were recorded, including anastomotic leaks, organ failure, septicaemia and multiple organ failure.

Results:

	Multimodal ($n=104$)	Surgery only ($n=108$)
30-day mortality	11 (11%)	11 (10%)
Major complications	38 (37%)	44 (41%)
Number of complications	56	73
Pneumonia	22 (21%)	29 (27%)
Anastamotic leaks	10 (10%)	8 (7%)
Sepsis/multiple organ failure	4 (4%)	9 (8%)
Organ failure	9 (9%)	5 (5%)
Abdominal/thoracic abscess	6 (6%)	2 (2%)

Conclusion: There was no significant difference between groups in complications that may relate to preoperative wound healing and immune competence. Fears that a price may be paid in the perioperative period for the oncological efficacy of multimodal therapy were thus unfounded in these randomized studies.

UGI 012

Conservative management of perforated duodenal ulcer: continuing audit and current guidelines

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Background: This study aimed to establish a protocol for conservative management of perforated duodenal ulcer (DU) with a continuing audit of the best practice guidelines.

Method: Thirty-six patients admitted between January 1991 and June 1997 with a perforated DU were treated conservatively according to protocol. Twenty further patients were excluded and treated operatively because they had generalized or deteriorating abdominal signs, a history of more than 24 h or were on antacid therapy. According to protocol all conservatively managed patients had a nasogastric tube and intravenous fluids, antibiotics and antacid therapy. Chest x-ray and gastrograffin confirmation of perforation were initially mandatory with discharge on antacid therapy and 6-week endoscopy.

Results: Of the 36 conservatively managed patients, 31 (86 per cent) had a history of less than 24 h; 35 (97 per cent) had a successfully placed nasogastric tube; antibiotics were given to 29 (81 per cent) and intravenous antacids to 30 (83 per cent); 34 (94 per cent) had an erect chest x-ray but only 16 (44 per cent) had a gastrograffin meal (five of which confirmed perforation). However, only 10 (25 per cent) had thromboembolic (DVT) stockings prophylaxis and 14 (39 per cent) subcutaneous heparin. Five patients failed conservative management and there were five complications. Only 19 (53 per cent) had follow-up gastroscopy which confirmed two gastric cancers.

Conclusion: We have found that perforated DU can be treated successfully and conservatively with a protocol that should be strictly followed. Audit reviews have strengthened the need for follow-up gastroscopy and DVT prophylaxis but dispensed with the need for gastrograffin confirmation and central venous monitoring.

UGI 013

The use of photodynamic therapy in the treatment of dysplastic Barrett's oesophagus

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Background: Photodynamic therapy (PDT) is a form of cancer treatment in which cell damage is achieved by the action of light on a photosensitizing agent. The aim of this study was to assess the value of PDT in the treatment of Barrett's oesophagus with low-grade dysplasia.
Method: Forty patients with biopsy-proven dysplastic Barrett's oesophagus were treated with PDT. All patients were given the photosensitizer aminolaevulinic acid (ALA) orally at a dose of 30 mg/kg. Four hours later, patients underwent endoscopy and administration of green laser light (514 nm) at a power density of 120 mW/cm^2 for 500 seconds (total energy 60 J). All treatments were performed under propofol sedation as day cases. All patients continued treatment with omeprazole 20 mg daily. Endoscopy and biopsies were repeated at 1 and 6 months, to assess the effect of treatment.
Results: A macroscopic response was seen in 33 out of 40 patients, with a median decrease in columnar epithelial area of 30 (range 0–90) per cent. Post-treatment biopsies showed no evidence of dysplasia in 39 out of 40 patients, with low-grade dysplasia remaining in one case. No significant side-effects were observed in any patient.
Conclusion: This study demonstrates that ALA-induced PDT provides safe and effective ablation therapy for Barrett's oesophagus. Further studies are required to increase the efficacy of this form of treatment.

UGI 014

Preoperative staging of upper gastrointestinal malignancy by endoluminal ultrasound

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Background: Accurate preoperative staging is essential in planning rational treatment approaches to upper gastrointestinal malignancy. Endoluminal ultrasound (EUS) has been reported to improve the accuracy of preoperative staging of these tumours and we have evaluated this technique since its introduction to this unit.
Method: Prospective evaluation of 59 patients (43 gastric and 16 oesophageal carcinoma; 41 men and 18 women) who underwent preoperative staging with EUS between May 1996 and October 1997. In all cases histological confirmation of disease stage was achieved and no patients received neoadjuvant therapy. Surgical treatment comprised 54 resections, four staging laparoscopy and biopsy and one open and close laparotomy. Preoperative evaluation by EUS was incomplete or impossible in five patients leaving 54 patients (41 gastric and 13 oesophageal carcinoma) for comparison of individual components of preoperative and final histological stage (1987 TNM staging).
Results: In 55 patients with upper gastrointestinal malignancy, EUS predicted the final histological T stage in 40 of 54 patients (accuracy 74 per cent) and the final histological N stage in 37 of 54 patients (accuracy 69 per cent).

	Gastric carcinoma ($n=41$)			Oesophageal carcinoma ($n=13$)	
	T1 & T2	T3 & T4		T1 & T2	T3 & T4
Sensitivity	73%	68%		88%	80%
Specificity	68%	73%		80%	83%
	N0	N1	N2	N0	N1
Sensitivity	100%	20%	56%	86%	83%
Specificity	65%	90%	87%	83%	86%

Conclusion: EUS is of value in preoperative staging of upper gastrointestinal malignancy, allowing correct identification of those patients who may benefit from neoadjuvant therapy prior to surgical resection.

UGI 015

Surgical outcome for vertical-banded gastroplasty for morbid obesity

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Background: The aim of this study was to determine the outcome of vertical-banded gastroplasties (VBG) for morbid obesity.
Method: One hundred consecutive gastroplasties were carried out on 19 men and 81 women between 1982 and 1997. A questionnaire was sent to all patients to establish their current weight and quality of life using specific questions related to lifestyle.
Results: The median preoperative weight was 133·6 (range 91·9–224) kg with a median body mass index (BMI) of 49 (32–76) which reduced postoperatively to a median weight of 108·2 (73–254) kg and a median BMI of 38 (27–81). There was one operative death caused by respiratory failure. The median follow-up time was 3·06 years (0–15·3). Of the 96 returned questionnaires, 85 per cent had lost weight, 15 per cent had gained weight since the operation. The quality of life questions showed that 74 per cent of patients considered their self esteem/confidence had improved as a result of the operation, with 26 per cent improving their employment situation. Seventy-two per cent consider the operation had helped control their weight and had altered their eating and exercise habits. Eleven patients (11 per cent) who lost weight considered the operation to have failed.
Conclusion: VBG represents a reliable and safe surgical option for patients in whom all other methods to control weight has failed: 85 per cent of patients lost weight, 72 per cent indicated an improvement in their quality of life.

UGI 016

Nurse practitioner for postoperative review of patients following oesophagectomy

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Background: Following an initial audit of the post-discharge needs of patients undergoing subtotal oesophagectomy for cancer, a hospital-based, community liaison nurse practitioner role was implemented. The purpose of this audit was to assess the impact of instituting this change and its potential for altering the nature of postoperative follow-up for patients.
Methods: Patients who had undergone subtotal oesophagectomy were visited at home within 6 weeks of discharge for informal interview. Thereafter, repeat visits were at the discretion of the patient and nurse practitioner. Patients were encouraged to contact the nurse practitioner if problems occurred between routine 3-monthly outpatient appointments. Quantitative assessment was made by comparing the actions made as a result of nurse practitioner contact with those made as a result of consultant outpatient attendance. Qualitative assessment was made by interview and questionnaire survey of patients and their relatives.
Results: Over a 12-month period, 97 outpatient attendances were recorded compared to 85 home visits by the nurse practitioner. Twenty-two (26 per cent) of the nurse practitioner visits resulted in an intervention (most commonly endoscopy and dilatation of benign anastomotic stricture) compared with only five (5 per cent) of clinic attendances (χ^2 = 15·53 1 df; $P<0.0001$). There were no emeregency admissions of this group of patients via an accident and emergency department or GPs in this period. Thirty-five of 40 patients responded to a questionnaire survey, all of

whom supported the nurse practitioner visits. A key-word analysis of patient interviews and questionnaire responses highlighted 'support', 'expert advice', 'invaluable link', 'comfort', 'understanding' and 'reassurance' and descriptions such as 'invaluable link between hospital, community services and family' and 'its good to know that (she) is there to ring at anytime'.

Conclusion: The role of a hospital-based nurse practitioner is strongly supported by patients treated for oesophageal cancer. This facility is generally the preferred route of contact for patients with oesophageal cancer and avoids delay or unnecessary use of emergency routes.

UGI 017

Adenocarcinoma of the oesophago-gastric junction in the Northern and Yorkshire region 1984–1993

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Background: Previous studies have demonstrated marked changes in the incidence of subsites of gastric and oesophageal cancer. The aim of this study was to identify whether this trend has continued in a large UK cancer registry and to evaluate the degree of misclassification under the existing system.

Method: The recently amalgamated Northern and Yorkshire Cancer registry was interrogated for all cases of oesophageal and gastric cancer occurring between 1984 to 1993. Data of year of registration, subsite (according to ICD 10 codes 1500–1509 and 1510–1519), histology, sex and age were recorded. Statistical analysis was performed using Spearman's rank correlation, χ^2- and t-tests.

Results: 22 300 cases were identified from an estimated population of 6·7 million. Overall the age-adjusted annual incidence of oesophago-gastric cancer fell from 36·2 to 30·1 per 100 000 in the 10-year period ($P<0{\cdot}001$). Oesophageal cancer increased from 9·22 to 10 per 100 000 ($P<0{\cdot}05$) due largely to the increased incidence of adenocarcinoma of the lower oesophagus (IGCA [International Gastric Cancer Association classification] Type 1 junctional cancers). The incidence of gastric cancer fell from 27 to 20·2 per 100 000 ($P<0{\cdot}05$). Cancer diagnosed at pyloric, antral, lesser curve, greater curve, body and fundus subsites all significantly fell in incidence ($P<0{\cdot}001$). The incidence of adenocarcinoma of the gastric cardia (IGCA Type 2 junctional cancers) did not significantly change although it increased in proportion from 34 per cent (1984/5) to 55 per cent (1992/3) of all gastric cancers (χ^2 = 11·962 4 df; $P<0{\cdot}05$). Throughout the 10-year period, the majority of cases of oesophageal (70·4 per cent) and gastric cancer (71 per cent) were recorded without any information about subsite.

Conclusion: Although the trends towards an increasing proportion of cancers at the oesophago-gastric junction reported in earlier studies have been confirmed in this study, the high incidence of imprecise subsite reporting must put the conclusions of this and other similar cancer registry studies in some doubt. Cancer registration must recognize 'junctional cancers' as distinct from other gastric and oesophageal subsites in order to monitor accurately the increase in this distinct group of oesophago-gastric cancers in subsequent studies.

UGI 018

The impact of a high dependency bleeding unit on surgical outcome in patients with bleeding peptic ulcer

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Background: The aim of this study was to determine the impact of a bleeding unit, with pre-set protocols on transfusion and surgical referral, on rates of surgery and surgical mortality in patients with bleeding peptic ulcers.

Method: Between October 1991 and October 1994 all patients with a suspected gastrointestinal bleed were admitted to a six-bedded bleeding unit serving a population of approximately 500 000. Patients were transfused per protocol until haemodynamically stable and thereafter endoscopy performed. Transfusions of greater than 4 units and significant re-bleeds were the principal indications for surgery.

Results: Six hundred and ninety-seven patients were found to be bleeding from peptic ulcers (duodenal ulcer 446, gastric ulcer 236 and stomal ulcer 15). Of these, 124 patients required emergency surgery (18 per cent). The commonest procedure undertaken was under-running of the ulcer and a truncal vagotomy and pyloroplasty ($n=68$) but simple under-running was performed in 13 and partial gastrectomy in 31. The operating surgeon was a consultant in 67 per cent and a senior registrar in 30 per cent of cases. The overall mortality for bleeding peptic ulcers was 5·3 per cent and the surgical 30-day mortality was 10 per cent. In all cases this was associated with severe co-morbid disease. The mean age of the patients who died was 80 years (range 68–90 years).

Conclusion: The low overall mortality and low surgical mortality seen in this unselected group of patients with bleeding peptic ulcers relates to aggressive resuscitation and diagnosis with early surgical referral when appropriate. These conditions are readily established within a specialized gastrointestinal bleeding unit.

UGI 019

The detection of response to chemotherapy using positron emission tomography in patients with oesophageal and gastric cancer

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Background: This study aimed to determine whether glucose metabolism, detected by fluorodeoxy-D-glucose (FDG) positron emission tomography (PET), was predictive of response to chemotherapy in patients with gastro-oesophageal cancers.

Method: Twelve patients with tumours of the gastro-oesophageal region were imaged with FDG-PET prior to commencing and following two cycles of chemotherapy. FDG uptake in tumours was quantified by Patlak analysis allowing comparison of the two scans. The images were compared with endoscopic, computed tomography (CT) and clinical evaluation of response to treatment.

Result: Changes in FDG uptake from the first to the second PET images ranged from a 15 per cent increase in activity to a 77 per cent decrease in activity. In 6/12 patients there was a decreased tumour FDG uptake following chemotherapy which corresponded with clinical and endoscopic evidence of response. In four of these cases there was also CT evidence of >50 per cent reduction in the tumour size. Of the six patients who had PET evidence of response, five underwent resection; two of these patients with stage III disease survived 12 and 20 months postoperatively, three remain disease free at 6–18 months follow-up. A further patient with liver metastases who responded is alive at 10 months. In six patients PET indicated either no change in FDG uptake or an increased uptake suggesting progressive disease. Five of these patients have developed recurrent disease within 6 months of treatment (two have died at 6 and 7 months). One patient with a recurrent tumour which remained stable on PET is alive at 9 months.

Conclusion: This study has shown that PET scanning may be able to detect response to chemotherapy in patients with gastro-oesophageal malignancy. An accurate means of determining response to preoperative chemotherapy could allow better patient targeting, i.e. selection of responders to continue with a full course of chemotherapy or of non-responders to abandon chemotherapy.

UGI 020

Preoperative manometric assessment of oesophageal dysmotility does not correlate with poor outcome after laparoscopic Nissen fundoplication

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Background: Oesophageal dysmotility has been regarded as a contraindication to Nissen fundoplication because of concern over postoperative dysphagia. There is, however, little published data to support this conjecture and the aim of this study was to determine the outcome of patients with normal motility and dysmotility undergoing laparoscopic Nissen fundoplication.
Method: A single centre prospective cohort study with 1-year follow-up, using dysphagia as the main outcome variable.
Results: Of 81 patients with preoperative manometry who underwent laparoscopic surgery, 48 had normal motility and 33 had oesophageal dysmotility (defined as percentage peristalsis, using 10 wet swallows, of ≤50 per cent and/or a mean distal pressure of <40 mmHg). Dysphagia was present preoperatively in 14/48 of patients with normal motility and 15/33 of the dysmotility group ($P=0·2$). At 3-month follow-up, new or worse dysphagia was present in 13/48 of the normal group and 4/33 of the dysmotility group ($P=0·17$). At 1 year the incidence of dysphagia was 6/48 (12 per cent) in the normal group and 5/33 (15 per cent) in the dysmotility group ($P=0·9$).
Conclusion: Preoperative manometric assessment of oesophageal motility does not correlate with postoperative outcome. Oesophageal dysmotility should not be regarded as a contraindication to laparoscopic Nissen fundoplication.

UGI 021

Review of a 13-year surveillance programme for columnar lined oesophagus

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Background: The aim of this study was to determine the incidence of adenocarcinoma (ADC) in columnar lined oesophagus (CLO) and to review our surveillance programme, because although the risk of cancer is well established, the magnitude of this risk is still controversial.
Method: Records of all patients with histologically confirmed CLO in our 13-year surveillance programme were examined retrospectively.
Results: A total of 357 patients out of 597 patients with CLO, entered a yearly endoscopy and biopsy surveillance programme. After a mean follow-up of 43 months, 12 patients, all with specialized epithelium, developed ADC (11 males), an incidence for males of 1 cancer per 67 patient-years and for females 1 cancer per 533 patient-years follow-up ($P<0·01$).
Conclusion: While the role of screening patients with CLO remains controversial, on the basis of this data there is no doubt that it is justified in male patients with specialized epithelium.

UGI 022

Lower oesophageal sphincter incompetence: a major component in gastro-oesophageal reflux disease

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Background: It is argued that in patients with significant acid reflux, manometric evaluation of the lower oesophageal sphincter (LOS) does not always reflect the severity of reflux or oesophagitis. In order to determine the relevance of stationary manometry, 77 patients referred for manometry and 24-h acid profile were compared with respect to their pH profile after manometric evaluation of the LOS.
Method: The 77 patients underwent stationary oesophageal manometry with a water perfused five-channel catheter. Sphincter pressure was recorded at the respiratory inversion point. An incompetent sphincter was defined by a mean resting pressure of <6 mmHg, an overall length of <2 cm, an abdominal length of <1 cm or any combination of these. pH monitoring was with an antimony electrode 5 cm above the LOS. Reflux disease defined as a DeMeester score of >14·8. Statistical analysis was by the Kruskal–Wallis test.
Results: Three groups were defined; 54 patients had a normal sphincter, of these 21 had no evidence of reflux (controls) and 33 had reflux disease (NR), 23 patients had defective sphincters and reflux disease (AR). The 24-h pH profile and the prevalence of endoscopic oesophageal injury were then compared between the groups.

	% time pH<4	% time upright reflux	% time supine reflux	Post-prandial events	Barrett's/ oeso-phagitis
Control	1·1 (0–1·5)	1·3 (0–2·6)	0 (0–0·2)	4 (0–8)	7%
NR	8* (6·0–11·9)	12* (8·9–16)	6·7* (0·2–8·2)	37* (14·9–37·5)	48%
AR	18*†(12·9–24)	16·6*†(7·1–26·2)	14·1*†(5·7–31·8)	18·5*†(9·5–37)	67%

Values are expressed as medians (IQR). $^*P<0·01$ vs controls, $^†P<0·01$ vs NR.

Conclusion: Patients with gastro-oesophageal reflux disease with mechanically defective LOS have the highest levels of oesophageal acid exposure. Compared with refluxers with good sphincters they are more likely to have supine reflux and the highest frequency of oesophagitis/ Barrett's and so are ideal candidates for anti-reflux surgery aimed at restoring normal sphincter function.

UGI 023

A comparative study of the presentation and outcome of adenocarcinoma and squamous cell carcinoma of the oesophagus

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Background: The aim of this study was to compare the clinical, pathological and prognostic characteristics of adenocarcinoma (ACA) and squamous cell carcinoma (SCC) of the oesophagus.
Method: Data were collected prospectively from patients with a histological diagnosis of oesophageal cancer between 1989 and 1996. Details of clinical presentation, endoscopic and pathological features, treatment and survival were compared between patients with ACA and SCC. Statistical analysis was performed using χ^2-squared, t-test and log-rank test.
Results: Three hundred and eighteen patients were studied (ACA = 172; SCC = 122). The male:female ratio was higher in patients with ACA (3·53:1 cf. 1·22:1; $P<0·001$). The mean age at presentation was no different [ACA = 66·33 (0·759) cf. SCC = 66·67 (1·116)]. Dysphagia was a more common presenting symptom in patients with SCC than ACA (115/122 cf. 143/172; $P=0·002$) and patients with ACA tended to have lower grades of dysphagia at presentation ($P=0·006$). A greater proportion of patients with ACA have had previous gastric surgery (36/171 vs 8/122; $P=0·0006$). A higher proportion of patients with ACA had a history of proton pump inhibitor ingestion prior to diagnosis (52/171 vs 15/121; $P=0·0003$). Smoking and alcohol intake were similarly common in both groups of patients. There was no difference in stage of disease at presentation. A similar proportion of patients of each histological subtype were treated by resection [55 per cent (ACA) cf 43 per cent (SCC)]. Survival was no different between histological subtypes overall and stage for stage according to treatment policy.
Conclusion: ACA shows a greater male predominance and is less likely to present with dysphagia than SCC. The higher incidence of previous gastric surgery and prior prescription of proton pump inhibitors suggest a different aetiology for adenocarcinoma of the oesophagus.

UGI 024

Survival following Ivor–Lewis oesophagectomy with two-field lymph node dissection

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Background: Patients with oesophageal carcinoma present frequently with advanced disease and only surgery offers the best palliation and the best chance of cure. The aim of this study was to examine survival and recurrence following a two-stage Ivor–Lewis oesophagectomy with two-field lymphadenectomy.

Method: A consecutive series of 107 patients undergoing oesophagectomy in this hospital under the care of one surgeon was analysed. A proforma was completed, data was collected prospectively and entered on to a database. All patients underwent a preoperative assessment to evaluate patient fitness and tumour resectability.

Results: The mean age (range) of patients was 62·1 years (40–77 years) and 80 (74·8 per cent) were men. Sixty-three patients (58·9 per cent) had adenocarcinoma and 39 (36·4 per cent) had squamous cell carcinomas. Three patients died in hospital following surgery giving an in-hospital mortality of 2·8 per cent. Patients were subdivided according to stage and the 2-year, 5-year and median survival are given below:

Stage	2-year survival %	5-year survival %	Median survival (months)
Carcinoma *in situ*	100	100	>48
I	82*	82*	>48
IIa	66	43	39
IIb	69	27	28
III	25	19	17
Node negative	70	52	>48
Node positive	35	19	19
Overall	52	35	26

*100% if 30-day mortality excluded.

Conclusion: Excellent survival can be achieved following surgery for oesophageal carcinoma and surgery with or without neo-adjuvant chemoradiotherapy is the gold standard for treatment of oesophageal cancer.

General 001

The surgical impact of adhesions

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Background: This study aimed to determine the long-term morbidity associated with postoperative adhesions following open abdominal and pelvic surgery.
Method: Scotland's NHS hospital admissions are recorded by the Scottish Patient Record Linkage system. This system allows detailed analysis of hospital activity throughout Scotland including follow-up of individual patients. It has sophisticated accuracy checks to ensure the quality and totality of the dataset. The total number of individuals who underwent an open abdominal or pelvic procedure in 1986 was defined. Disease (ICD9) and procedure (OPCS3/4) codes for adhesion-related problems or reoperations that might be complicated by the presence of adhesions were identified. For the purposes of the study only codes for directly related adhesions complications were selected (e.g. small bowel obstruction and adhesiolysis). These were then used to identify those individuals who had admissions and possibly procedures directly related to postoperative adhesions over the next 10 years. The study was steered by a multidisciplinary panel of surgeons, gynaecologists and health economists.
Results: In 1986, a total of 29 788 patients had surgery in Scotland that was considered likely to cause adhesions. During the next 10 years 10 325 individuals (34·7 per cent) required one or more readmissions for surgical or medical treatment for conditions either related to adhesions or involving a reoperation which could be complicated by adhesions. 21 342 surgical or medical readmissions were identified in these patients; 1169 (5·5 per cent) of these admissions were identified as a direct result of abdominal or pelvic adhesions (3·9 per cent of all initial operations). This constituted a large clinical burden throughout the study period. Considerable variation in the rates of readmission was seen when the site of the initial surgical procedure was analysed.

			Readmissions directly attributable to adhesions		
Site of initial surgery	No. patients	Total no. readmissions	Total number	% of all readmissions	% of initial surgery
Lower GI	12 585	8861	627	7·1	5·0
Upper GI and 'other abdominal'	8714	7048	321	4·6	3·7
Gynaecological	8489	5433	221	4·1	2·6
Total	29 788	21 342	1169	5·5	3·9

Conclusion: The study provides the first epidemiological assessment of post-surgical adhesions and using an extremely conservative view, the impact of adhesions, both medical and surgical, is considerable, with 5·5 per cent of readmissions over a 10-year period directly attributable to adhesions. The full impact of adhesions, including their effect on subsequent surgery, is likely to be considerably greater and extensive research is in progress to investigate the burden further.

General 002

External oblique aponeurosis nerve entrapment as a cause of groin pain in the athlete

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Background: Groin pain in sportsmen is a common diagnostic and management problem. We describe the findings and results of surgical exploration in 25 athletes.
Method: All patients were male, age range 20–35 years, and had had failed conservative management. All groins were explored via an inguinal incision. The patients were reviewed with regards to pain, function, and their own subjective assessment of the operation.
Results: Nineteen cases were unilateral and six were bilateral. In one patient an occult inguinal hernia was found, and one patient had a patent processus vaginalis. In all patients defects were found in the external oblique aponeurosis through which neurovascular bundles, which contained the terminal branches of the iliohypogastric nerve, passed. These defects were closed after division of the neurovascular bundles. The mean delay from the time of injury to referral was 29·3 weeks (range 4–79 weeks) during which each patient had unsuccessful conservative treatment. The mean follow-up for the patients was 20·6 months (7–56 months). Postoperatively no pain or only mild pain was experienced in 28 groins and the function had improved in all. Eighty-eight per cent of the patients described the operation result as good or excellent with all of the patients returning to full sporting activities within 11·6 weeks (range 4–20).
Conclusion: We believe that athletes' groin pain may be due to nerve entrapment in the lower part of the external oblique aponeurosis. We suggest that an awareness of the symptomatology and the benefits of surgery may lead to early surgical exploration and, therefore, early resumption of sporting activities.

General 003

Driver reflex times following open and endoscopic 'tension free' hernia repair

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Background: One of the most frequently asked questions following inguinal hernia repair is when the patient can return to driving a car. The current recommendation, based on a study of plication darn-type repair, is that the patient should not drive for 10 days.
Method: The aim of this study was to measure both hand and foot reaction times in a car simulator. Sixty-four patients randomized to open and endoscopic 'tension-free' hernia repair were studied. The reaction times were measured preoperatively and at 1, 3 and 6 days postoperatively.
Results: There was no difference between the groups in age, sex or site of hernia. No significant difference was found in hand reaction times between the groups on each of the postoperative days. The mean changes in foot reaction times are shown below in milliseconds and are expressed as positive (slower) or negative (faster) in relation to preoperative values.

Day	Open	Endoscopic	*P* value
1	30·6	–4·2	0·01
3	32·5	–10·4	0·003
6	–7·0	–16·9	0·27

Conclusion: The significant decrease in reaction times in the open group at days 1 and 3 appears to be due to a combination of a delay in response caused by analgesics and an increase in the transfer time due to discomfort from the operation site. These results provide objective evidence that endoscopic hernia repair allows a faster return to normal activities than open 'tension-free' repair. Patients undergoing open or endoscopic 'tension-free' inguinal hernia repair can return to driving within 1 week of operation.

General 004

Dynamic magnetic resonance imaging: a new diagnostic modality for groin pain?

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Background: Existing diagnostic modalities are either invasive or insufficiently sensitive to distinguish reliably occult inguinal hernia from musculotendinous injury as a cause of groin pain. This may result in a high negative surgical exploration rate. The aim of this study was to develop a non-invasive dynamic magnetic resonance (MR) technique to differentiate these lesions.
Method: Eleven patients (nine men, two women; age range 29–73 years; median age 43 years) were studied in a 0·5 T General Electric Signa SP interventional magnetic resonance (IMR) unit. One patient had a persistent painful groin swelling 3 months after open mesh hernia repair and 10 presented with groin pain without physical signs (one had had a previous inguinal hernia repair). Static imaging [T1 fast spin echo (FSE), fast gradient recalled (FSPGR) and short tau inversion recovery (STIR)] was performed supine for detailed anatomical examination and differentiation of structural from inflammatory lesions. Dynamic real time imaging (FSPGR, acquisition time 2 s) was then performed supine, kneeling at rest and during a Valsalva manoeuvre to assess inguinal canal integrity with muscular exertion in a physiological position.
Results: All patients tolerated the procedure. In the 10 without physical signs, imaging revealed one indirect sac (male, 30 years) and one recurrent direct sac (male, 60 years). Defects in the fascia transversalis were clearly delineated and the sacs could be seen herniating through these defects on Valsalva manoeuvre. STIR images in these cases were normal. Seven others demonstrated high signal on STIR images in the posterior rectus muscle, conjoint tendon or at the pubic insertion of the inguinal ligament. No hernial defect was demonstrated in these cases. These findings were consistent with musculotendinous injury. No abnormality was demonstrated in the final case with groin pain (male, 24 years). The lesion in the patient with persistent groin pain and swelling after previous repair was demonstrated to be a cord haematoma and not a recurrent hernia by high signal on T2 and STIR imaging.
Conclusion: This study has demonstrated that dynamic MR imaging in physiological positions can detect and differentiate occult groin hernia from musculotendinous injury. This may reduce the high negative surgical exploration rate for such patients in the future.

General 005

Shouldice inguinal hernia repair revisited: a prospective, randomized trial of non-absorbable versus absorbable suture

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Background: This study aimed to assess the efficacy of long-term absorbable (Maxon: polyglyconate) suture compared with standard absorbable (Prolene: polypropylene) in shouldice inguinal herniorrhaphy. It further aimed to revisit a standard method of repair and assess recurrence, particularly with reference to type of suture and grade of surgeon.
Method: Patients undergoing elective repair of inguinal hernia were randomized to have either non-absorbable (Prolene) or absorbable (Maxon) suture as part of a standard shouldice procedure. All operations, if not performed by a consultant surgeon, were done by a junior after a suitable period of instruction in the technique as used at this hospital. Most repairs were as day cases. All patients were followed up at 6 weeks, 6 months, 1 year and 5 years postoperatively to assess complication and recurrence rates.
Results: Almost 400 patients have been entered into the trial of whom 339 were available for the study. Mean age was 57·2 years, range 19–88. Most were men (327) and 62 (19 per cent) were smokers. Two hundred and twenty (64·9 per cent) were day patients; 170 operations were performed by a consultant, 130 by a registrar, five by a staff surgeon and 34 by a senior house officer. One hundred and sixty-two had Maxon while 177 had Prolene. So far, 301 patients (88·8 per cent), have been followed for at least 1 year. The complication rate has been acceptably low with wound pain on first outpatient visit being the most common problem (5 per cent). There have been five recurrences (1·4 per cent) but no differences between either suture. Grade of surgeon did not alter outcome.
Conclusion: Shouldice repair of inguinal hernia remains a very effective operation which can be performed as day cases with acceptably low complication and recurrence rates in a district hospital. Type of suture or grade of surgeon, once properly taught, did not adversely affect outcome in this study.

General 006

Cyclical or continuous peripheral parenteral nutrition: a 10-year review

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Background: Peripheral parenteral nutrition (PPN) is usually prescribed as a 24-h continuous infusion. However, cyclical administration may be associated with a reduced venous morbidity.
Method: Retrospective review of 10 years' nutritional practice in a district general hospital comparing morbidity of cyclical and continuous infusion of PPN.
Results: A total of 694 patients received PPN, as a continuous infusion in 455 (66 per cent) and cyclically over 12 h in 234 (34 per cent). Catheter-related sepsis occurred more frequently in the continuous than in the cyclical group (9·2 per cent versus 0·4 per cent, $P < 0{\cdot}02$). Phlebitis was twice as common in the continuous PPN group compared to cyclical infusion (5·9 per cent versus 2·8 per cent). Fluid overload occurred in 51 patients (7·3 per cent) in the series and was unrelated to infusion method. There were biochemical differences between the two groups.
Conclusion: Morbidity is higher with continuous infusion than with cyclical infusion. Cyclical infusion is the optimal method of giving PPN to gastroenterological patients.

General 007

The treatment of subungual melanoma with isolated limb perfusion: a 10-year experience

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Background: Subungual melanoma is rare and reports in the world literature of treating this condition with isolated limb perfusion (ILP) are limited. We present our 10-year experience of this condition.
Method: Thirty-two patients (14 men, 18 women) were treated with digital amputation and ILP using melphalan and mild hyperthermia. The disease was staged according to the M. D. Anderson Classification.

Results: Stage I (21 patients), stage IIIA (four patients), stage IIIB (three patients) and stage IIIAB (four patients) made up the study group. Nineteen lesions were on the foot and 13 on the hand. There was no operative mortality Of 21 patients with stage I disease, at mean follow-up of 46 months, 14 are alive and disease free and one is alive with disease. Five patients with stage I disease have died of disseminated disease and one was disease free at death from another cause However, the prognosis in stage III patients is poor, with only two survivors at 18 and 28 months.
Conclusion: It appears that ILP using melphalan and mild hyperthermia confers no additional survival benefit over appropriate surgery in stage I disease It does not significantly reduce disease-free suvival in stage III disease

General 008

A phase II evaluation of the Marlex plug hernia repair

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Background: Lichtenstein and laparoscopic inguinal hernia repairs, whilst an improvement on previous techniques, have associated postoperative pain, expense, and complications, including intraperitoneal trauma A new technique for inguinal and femoral herniae involves insertion of a Marlex plug into the hernial orifice, with a modified mesh overlay.
Method: Minimally invasive, through a 4 cm incision, and extraperitoneal, a Marlex plug requires non-periosteal absorbable stay sutures only A 7-month phase II trial was conducted on 40 patients (39 men, 1 woman, median age 64 years [range 26–90]).
Results:

Inguinal hernia	37 (24 indirect, 12 direct, 1 directo-indirect)
Femoral hernia	3
General anaesthetic	22
Local anaesthetic	17
Spinal anaesthetic	1
Median operation time (range)	35 (7–59) min
Median duration hospital stay (range)	24 (8–96) h
Median days until totally pain free (range)	6 (1–77) days
Median return to normal activity (range)	10 (1–84) days
Median return to work (range)	28 (3–56) days

Complications included three haematomas, conservatively managed and one failure of resolution of preoperative symptoms. There were no recurrences. Our results indicate that the plug repair is minimally invasive, quick, and gives excellent overall patient satisfaction
Conclusion: Patients are rapidly pain free, facilitating early return to normal activity. We believe a phase III randomized controlled trial of plug vs Lichtenstein repair is now needed.

General 009

How much do trainers train? An objective assessment

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Background: The aim of this study was to assess consultant supervision in general surgery.
Method: Details of trainee experience and consultant supervision for five general surgical operations performed under 17 consultants were retrieved from a prospective database
Results: Consultants assisted trainees in only a small proportion of the available operations. Supervision by individual consultants varied widely

		Consultant assisting		
Operation	No operations	Registrar [mean % (range)]	SHO [mean % (range)]	Unsupervised trainee [mean % (range)]
Inguinal hernia	740	6 (0–18%)	10 (0–52%)	50 (6–90%)
Varicose veins	719	10 (0–42%)	7 (0–28%)	40 (5–100%)
Right hemicolectomy	150	31 (0–52%)	3 (0–22%)	34 (0–100%)
Hartmann's	43	21 (0–60%)	0	23 (0–67%)
Laparoscopic cholecystectomy	552	27 (14–65%)	5 (0–17%)	28 (14–65%)

Conclusion: This study suggested many potential training opportunities were not used. The variation in consultant supervision suggests a minimal level of training should be defined

General 010

Corneal contamination during laparoscopic cholecystectomy

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Background: This study aimed to assess whether contamination of the cornea during laparoscopic cholecystectomy may occur. Infective agents such as human immunodeficiency virus, hepatitis B and C have all been implicated in blood-borne transport from patients to medical staff, of these, hepatitis B has been documented as transmitted by corneal contamination in a non-surgical case.
Method: Protective glasses were worn by a single operator for 20 consecutive laparoscopic cholecystectomies. The length of procedure and awareness of operator to facial splashes was recorded before inspection of the lenses. The number of droplet splashes was counted at the end of the operation
Results:

Outcome (patients)	Mean droplets	Surgeon aware	Surgeon unaware
Splashes 14	4 2 (range 1–12)	1 operation	13 operations
No splashes 6			

Splashes over the glasses occurred in 14 operations (70 per cent). In those cases where splashes occurred there was a mean of four droplet marks (range 1–12) The operator was only aware of facial splashes in one patient (7 per cent) where splashes had occurred on the glasses.
Conclusion: There is a real risk of corneal contamination during laparoscopic cholecystectomy We recommend that surgeons and assisting theatre staff wear eye protection during all laparoscopic procedures.

General 011

Delays in emergency surgery: a prospective audit

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Background: National Confidential Enquiry into Perioperative Deaths (NCEPOD) guidelines suggest that our provision of emergency surgical treatment needs to be improved The objective of this study was to assess the reasons behind delays in taking emergency surgical patients to theatre.
Method: A single surgical firm audited all its emergency operations over a 3-month period, the findings were discussed at the departmental audit meeting and changes in clinical practice implemented over the following 2 months The same firm then re-audited its emergency operations over a subsequent 3-month period Significant delay was defined as a time lapse of more than 2 h between the decision to operate and actual time of the patient entering theatre. Between the two audits, the surgical rota was altered so

that there was always a surgeon of appropriate grade available for emergency surgery. This surgeon was released from other commitments such as outpatient clinics and elective lists. The theatre manager made provision for a theatre dedicated to general surgery throughout the day to attend to emergencies and semi-emergencies only. The audit loop was closed.
Results: The total number of patients in the two analyses was 45 and 54, respectively. Initial audit revealed significant delay in 26 (58 per cent); the main reason being lack of theatre staff in nine (35 per cent) cases. Subsequent audit showed a delay in 30 (56 per cent), but theatre staff delays fell to six (20 per cent) cases. Initial figures indicated that 38 per cent of operations were done between 0900 and 1700 h, and this rose to 45 per cent on completing the audit cycle.
Conclusion: These are problems that beset most district general hospitals. Our study has shown that a dedicated emergency theatre team as well as co-operation between surgeons, anaesthetists and theatre staff can improve clinical standards.

General 012

The visceral slide technique for assessment of abdominal wound adhesions

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Background: This study aimed to assess the role of the visceral slide technique in identifying intra-abdominal adhesions to the undersurface of abdominal wounds.
Method: The visceral slide technique has recently been described. Using a 7-MHz linear array ultrasound transducer the movement of the viscera directly beneath the abdominal wall is measured during exaggerated respiration. A slide of 2–5 cm of the viscera relative to the abdominal wall is considered normal, while a slide of 1 cm or less implies tethering of the viscera to the back of the abdominal wall and is strongly suggestive of adhesions.
Results: A total of 36 visceral slide ultrasound scans have been performed on 28 patients, of whom 18 had been referred for assessment of chronic abdominal pain attributed to adhesions. The remaining patients had laparotomies as part of a study into a new bioresorbable anti-adhesion membrane. Fifteen scans were performed preoperatively and 19 scans were performed postoperatively. The postoperative scans were performed at a mean of 6 weeks. Of the 15 preoperative scans, six suggested adhesions to the previous abdominal wound, five no adhesions present and in four the result was uncertain. The uncertain results were in wounds in the suprapubic region where the effects of exaggerated respiration are minimal. Eleven of these 15 patients went on to laparotomy and division of adhesions. In the seven patients with a definitive scan result, the visceral slide technique correctly identified the absence or presence of adhesions in five patients and was partially correct in two patients. There were 19 postoperative scans. Nine scans were performed in patients following laparotomy and division of adhesions. Eight out of the nine scans were negative for adhesions. The one patient with a positive adhesion scan after laparotomy was also the only patient to report a worsening of his symptoms.
Conclusion: The visceral slide technique is a reliable, quick and non-invasive method for assessing the presence of abdominal adhesions to the undersurface of previous laparotomy wounds. It also has a potential role in evaluating the effectiveness of adhesiolysis surgery.

General 013

24-hour access to a surgical database on CD-ROM has both educational and patient management benefits

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Background: The aim of this study was to determine whether 24-h access to current surgical literature via a personal computer CD-ROM is of relevance to the junior surgeon managing acute surgical referrals.
Method: Over a 2-month period, a single basic surgical trainee assessed 53 acute surgical referrals. *Silver Platter* software was used to search the *Medline* database using one or two keywords for relevant information that would be of educational value and enhance patient management.
Results: Forty-nine per cent of database enquiries were made outside the hours 1700–0900. Thirty-eight per cent of all enquiries increased trainee knowledge and a further 17 per cent changed patient management. Forty-five per cent of searches did not reveal useful information. The most frequent enquiries regarded symptom aetiology (38 per cent), choice of antibiotics (19 per cent) and complications (19 per cent).
Conclusion: 24-h access to a surgical database on CD-ROM is a practical tool for the on-call basic surgical trainee and was found to have a large educational value together with a smaller but significant role in enhancing patient management.

General 014

Artificial neural networks for the prediction of recurrence of oesophagogastric junction cancers

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Background: Identification of patients who are destined to suffer early recurrence, following radical surgical resection of cancer of the oesophago-gastric junction, is important to rationalize management decisions. We evaluate the ability of an artificial neural network to predict, using preoperative information alone, those patients destined to have recurrence within 1 year of surgery.
Method: Data from 103 patients undergoing potentially curative resection of adenocarcinoma of the oesophago-gastric junction were collected prospectively. A three-layer artificial neural network system was used. Preoperative data included gender, age, site of cancer, planned operative approach (two-stage Ivor–Lewis oesophagectomy, transhiatal, transabdominal gastrectomy with or without splenectomy or pancreatectomy) and grade of cancer from biopsy specimen were used as input variables. A separate network was designed for use with selected additional postoperative variables including depth of invasion, neural invasion, vascular invasion, resection margin clearance, positive longitudinal resection lines, nodal status and total number of lymph node groups involved. Forty-three patients were used to train the network and 60 were used to test the system.
Results: Five patients in the test group developed recurrence. This was correctly predicted in all cases using preoperative data alone. Specificity was 60 per cent and accuracy 63 per cent. By including postoperative variables, sensitivity was maintained at 100 per cent but specificity and accuracy increased to 73 per cent and 75 per cent, respectively. There was a strong correlation between the predictive value of pre- and postoperative findings in individual patients (correlation coefficient = 0·6333: $P < 0 \cdot 0001$).
Conclusion: Artificial neural networks are able reliably to predict, even with limited clinical preoperative information, patients destined to fail when treated by surgery alone. This approach may have a role in assisting clinicians to achieve more appropriate selection of patients for surgery and neo-adjuvant therapy.

General 015

Neural networks as an aid in the diagnosis of acute appendicitis

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Background: The aim of this study is to assess the effectiveness of a neural network in the diagnosis of acute appendicitis in patients presenting with right iliac fossa (RIF) pain.
Method: Retrospective data, with regards to age, sex, symptoms, signs and investigations as previously used in other scoring systems, of 15

patients with acute appendicitis and 15 patients with histologically normal appendices presenting with RIF pain were used to train the Weightless Advanced Neural Device. The symptoms, signs and investigations that were used were migratory RIF pain, nausea, anorexia, RIF tenderness, rebound tenderness, temperature, white cell count and differential. All patients had a preoperative diagnosis of acute appendicitis. The neural network was then tested with 20 further patients with a known diagnosis of a normal or an inflamed appendix with varying retinal coverage and number of neuronal inputs.

Results: The neural network was shown to have a 100 per cent specificity and sensitivity in the diagnosis of acute appendicitis using these data, which compares favourably with other diagnostic aids and scoring systems. These results were repeatable each time the network was built. It was shown that the neural network was able to reach the diagnosis with greater confidence when increasing numbers of neuronal inputs were used: confidence range with four neuronal inputs was 0–9 per cent and 3–30 per cent with eight inputs. Confidence was further improved with random neuron coverage when compared to horizontal coverage.

Conclusion: We have shown that this neural network can distinguish between patients with and without acute appendicitis presenting with RIF pain who underwent surgical exploration. Further evaluation will be required to determine if it can predict which patients presenting to the Accident and Emergency Department with acute RIF pain will require surgery.

General 016

Artificial neural networks for the prediction of outcome following surgery for gastric cancer

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Background: An artificial neural network (ANN) is a form of artifical intelligence that is able to learn non-linear relationships between data and use this knowledge to answer questions about further data to which it has not been exposed. We decided, therefore, to compare a neural network analysis with the traditional statistical approach for the prediction of outcome following surgery for gastric cancer.

Methods: ANNs were designed with 60 input variables in the first layer, 0, 2, 3, 4, 5, 6, 7, 15, 20, 25 or 30 hidden 'neurones' in the second layer and a simple positive negative output. Data from 183 patients were utilized: 133 to train and 50 to validate each ANN for the prediction of death at 12 months. The neural networks were then compared against traditional multivariate analysis on 10 randomly selected validation data sets.

Results: The ANNs achieved a mean sensitivity of 0.62 (range 0.61–0.65) and a specificity of 0.77 (range 0.73–0.79) with a mean overall accuracy of 0.71 (95% C.I. 0.57–0.83) as opposed to the traditional multivariate analysis which achieved a mean sensitivity of 0.56 (range 0.43–0.79) and specificity of 0.68, range 0.52–0.85 with a mean overall accuracy of 0.62 (95% C.I. 0.49–0.75). There was no statistically significant difference between the two methods of analysis although the ANNs were significantly more robust and consistent in their prediction.

Conclusion: The failure to improve on the accuracy of the traditional linear statistical methods may be due to either too small a learning set, too simple a problem or the absence of any underlying pattern in the data and further work is therefore required. This accepted, in practical terms, ANNs are able to provide a more consistent method of prediction of outcome gastric following gastric cancer surgery.

Vascular 032

The effect of intraoperative autologous leucodepletion upon leucocyte counts and levels of neutrophil activation

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Background: Neutrophils (PMNs) are integral to the pathogenesis of ischaemia reperfusion injury (IRI) and PMN depletion by both mechanical and immunological methods has been shown to ameliorate this injury in animal models. A clinical assessment of these techniques has not been performed.
Method: In 10 patients undergoing limb salvage surgery, the effect of PMN depletion (using a double-lumen femoral venous catheter, extracorporeal circuit, leucocyte filter, and flow rates of 200 ml/min for 15 min [3000 ml or ~60 per cent blood volume filtered]) upon PMN, monocyte and lymphocyte counts, adhesion molecule expression (CD11b, CD18, L-selectin) and myeloperoxidase (MPO) levels was compared with changes in 10 control patients (CP) undergoing similar surgery. Samples were taken from both peripheral (PER) and femoral (FEM) venous blood at baseline and at reperfusion, 4 h, 24 h, 3 and 6 days (T_0, T_4, T_{24}, T_{3D}, T_{6D}).
Results: PMN were effectively depleted from the filtered blood from 4·04 × 10^9/L (range 2·55–5·75) [median and IQR] to 0·72 × 10^9/L (0·42–1·30) [P=0·002], and 1·08 × 10^9/L (0·10–1·89) [P=0·012] following 5 and 15 min of filtration, respectively. Monocyte counts also fell from 0·30 × 10^9/L (0·20–0·46) to 0·03 × 10^9/L (0–0·20) [P=0·004] at 5 min and 0·075 × 10^9/L (0·03–0·10) [P=0·09] at 15 min. Similarly lymphocyte counts were reduced from 1·45 × 10^9/L (1·09–1·9) to 0·1 × 10^9/L (0·08–0·22) at 5 min and 0·95 × 10^9/L (0·58–1·3) at 15 min (P<0·0001 at both points). PMN adhesion molecule expression was always lower in filtered patients (both FEM and PER), and was significant for CD11b at T_0 FEM (P<0·0001), T_4 PER (P=0·0195), T_{24} FEM (P=0·0012) and T_{3D} (P=0·0140). The reduction in CD18 expression was significant at T_0 PER (P<0·0001) and T_{24} FEM (P=0·0311), while falls in L-selectin were significant at T_4 PER (P=0·0072). Levels of MPO were higher in the filter group at T_0 FEM (P<0·0001) and T_4 FEM (P<0·0001).
Conclusion: This novel study of intraoperative PMN depletion shows a favourable reduction in activated neutrophils, that may ameliorate IRI. The incidence of infective complications, amputation and death were comparable between the two groups. In patients undergoing limb revascularization, this technique is safe, and the results suggest that further investigation is warranted.

Vascular 033

Vascular surgical intervention following complications of cardiovascular radiology: 13 years' experience in a single centre

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Background: This study investigates incidence and outcome of iatrogenic radiological vascular complications in a single vascular unit. Evolution of diagnostic and interventional cardiovascular radiology, along with introduction of non-surgical therapies for such complications, may have influenced the number of vascular complications requiring emergency surgery.
Method: Vascular surgical data were collated from information prospectively entered on computerized database and case-note review. Radiology data were collated from prospective entries in logbooks and a computerized database.
Results: A total of 24 033 cardiovascular radiological procedures were performed between 1984 and 1996 (61 per cent cardiac) with numbers increased annually. During this period 62 patients (40 peripheral; 22 cardiac) required emergency surgical intervention following radiological procedures. Mean (range) age was 62 (1–92) years, male to female ratio was 1:1. Number of cases requiring surgical intervention peaked in 1989 (0·7 per cent), subsequently reducing annually (0·18 per cent in 1996). Sites of vascular injury included common femoral artery (66 per cent), brachial artery (7 per cent), iliac artery (6 per cent), popliteal artery (4 per cent), other (17 per cent). Eighty-seven vascular surgical operations were performed (range 1–6 operations per patient). Interventions included thrombectomy/embolectomy (29), bypass grafting (16), direct repair (27). Seven major amputations were performed (two bilateral). Mortality following surgery was 9·7 per cent. Mean (range) inpatient hospital stay was 11·3 (0 to 75) days. A Poisson regression model indicated a 5 per cent reduction in risk for each successive year of observation, however, this did not reach statistical significance (P=0·16, 95 per cent CI 12 per cent decreased risk, 2 per cent increased risk).
Conclusion: The risk of surgical intervention following diagnostic or interventional cardiovascular radiology is diminishing. Surgical intervention is associated with a high risk of morbidity and mortality.

Vascular 034

How accurately recorded are OPCS codes for vascular surgery?

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Background: Centrally recorded OPCS codes are based upon district returns. The aim of this study was to determine the accuracy of this system with regard to vascular surgery.
Method: Prospectively recorded audit data for vascular and endovascular procedures were compared with those obtained from the Department of Health and Welsh Office. Five UK hospitals were involved in the study. Data were obtained for the 12 months between April 1994 and March 1995.
Results: The total number of arterial reconstructions based on audit data was 648. Those recorded by the OPCS codes were 477. This represents a discrepancy of -26 per cent (range -13·1–63·8 per cent). When examining specific codes, similar discrepancies were seen. For example, in one hospital 38 AAA repairs were carried out but only two were centrally recorded. However, examination of ICD9 codes (relating to hospital admissions) for that hospital showed that 38 patients with AAA were admitted. A similar wide variation was seen when examining iliac and superficial femoral artery endovascular procedures. Despite the discrepancies of audit and OPCS data, broadly the codes did reflect the relative workload of the different hospitals.
Conclusion: This study shows that there is a marked underestimate of vascular workload when comparing central recorded data with that obtained from local audit. Marked variation is seen in the accuracy of data submitted from different hospitals.

Vascular 035

The impact of MRSA in vascular graft infections

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Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a significant pathogen because of resistance to current anti-

biotics. Our aim was to determine incidence of, and outcome after MRSA vascular graft infections in a single centre over 12 years.
Method: Patients undergoing arterial bypass procedures since January 1985 were identified from a computerized database. Case notes of patients with graft infections were analysed for potential risk factors. Limb and patient outcome were analysed with respect to primary operation, graft type and bacterial culture.
Results: A total of 2096 bypass operations were performed. Thirty-six graft infections occurred in 30 men and six women after a median of 8 months (range 10 days–7 years). Fifteen patients were operated on for claudication, 14 for critical ischaemia and seven for an aneurysm. Of 25 monocultures, seven were MRSA. MRSA also occurred in two patients as part of a mixed culture. The primary operations were 17 aortic, 10 infra-inguinal and nine extra-anatomic grafts. Eight patients had percutaneous transluminal angioplasty, 23 had dacron and five vein grafts. Death was most common after aortic graft infection (8/17) and dacron in graft infection (13/23), while amputation was more likely to follow infrainguinal infection (4/10) and vein graft infection (3/5). There were three deaths and three amputations in nine patients with MRSA infection compared to five deaths and two amputations in 12 patients with non-MRSA *staphylococcus aureus* infection.
Conclusion: MRSA is now a common cause of vascular graft infection in this hospital but the prognosis for life and limb is not worse compared to graft infections with non-MRSA bacteria.

Vascular 036

Randomized trial of rifampicin-bonded Dacron grafts for extra-anatomic vascular reconstruction: early results

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Background: Serious infection complicates a small proportion of prosthetic vascular grafts and usually follows implantation of bacteria at the time of graft insertion. The aim of this study was to determine whether the use of a rifampicin-bonded gelatin-coated Dacron graft (Gelsoft or Gelseal, Vascutek Ltd) could reduce the rate of infective complications after bypass.
Method: In a multi-centre study involving 14 vascular units, 257 patients underwent extra-anatomic bypass (femorofemoral 149; axillofemoral 80; cross iliofemoral 28) for claudication 46 per cent, ischaemic rest pain 28 per cent, gangrene 20 per cent or acute ischaemia 6 per cent. There were 178 men and 79 women, median age 69 years, range 43–92.
Results: One hundred and thirty-two patients (51 per cent) had no recognized risk factors for wound or graft sepsis; 82 (32 per cent) had one and 43 (17 per cent) two or more risk factors. Patients were randomized 1:1 using sealed envelopes to rifampicin bonding (1 mg/ml rifampicin soak for 15 min prior to insertion) or controls. Routine 3 shot antibiotic prophylaxis was administered according to local protocol. Follow-up is complete to 1 month. One hundred and twenty-three patients had rifampicin-bonded grafts and 134 were controls. No side-effects were noted from Rifampicin bonding. A total of 200 patients made an uncomplicated recovery [77 per cent bonded vs 78 per cent controls, $P = 0{\cdot}8287$ (χ^2 test)]. Median duration of hospital stay was similar in both groups: 10 days, range 1–79. There were 18 (7 per cent) perioperative deaths (9 per cent bonded vs 5 per cent controls, $P = 0{\cdot}2432$). There were two early graft infections (both in the unbonded group). Rifampicin-bonded grafts had the following advantages: reduced total incidence of wound complications, e.g. erythema/discharge/dehiscence (16 per cent vs 22 per cent, $P = 0{\cdot}2151$), reduced need for a post-operative course of antibiotics (13 per cent vs 18 per cent, $P = 0{\cdot}2788$) and fewer patients with delayed hospital discharge (7 per cent vs 11 per cent, $P = 0{\cdot}4077$).
Conclusions: Despite the fact that the main advantage of antibiotic bonding is expected to be a reduction in late graft infection, there were reductions in minor postoperative infective complications which alone may justify the (small) expense of rifampicin bonding.

Vascular 037

The surgical management of renal artery stenosis in children

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Background: The aim of this study was to assess the outcome of treating paediatric renovascular hypertension surgically.
Method: The study was a retrospective analysis of recent experience at one teaching hospital.
Results: There were nine young patients, median age 19 years (range 3–22). Presentation was asymptomatic hypertension (4), headache (3), claudication (1) and hypertensive encephalopathy (1). Initial median diastolic pressure was 100 mmHg (range 90–115); systolic pressure was 160 mmHg (range 130–185). Four had ECG changes of left ventricular hypertrophy. Arterial lesions were: isolated renal artery stenosis (6), mid-aortic syndrome (2), neurofibromatosis (1). Median time from diagnosis to treatment was 7 months (range 3–36). Balloon angioplasty was successful in one patient and failed in two. Operations performed included aorto-renal graft using saphenous vein/internal iliac artery/dacron (3), aorto-aortic graft with simultaneous renal revascularization by vein graft/direct reimplantation (2), spleno-renal bypass (1), renal autotransplantation (1). All patients were normotensive at discharge. Median follow-up was 2 years (range 2 months–11 years). Median time to stopping antihypertensive medication was 6 months (range 0–23). One patient needed secondary surgical intervention after 9 years for recurrent hypertension (patch to coeliac origin stenosis in patient with spleno-renal bypass). One 8-year-old girl with mid-aortic syndrome is currently awaiting surgery.
Conclusion: Renal revascularization for hypertension in the young patient is effective and durable. We advocate early intervention rather than waiting for systemic manifestations.

Vascular 038

The local delivery of rifampicin from a collagen carrier for the control of prosthetic infection

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Background: The aim of this study was to evaluate the efficacy of locally delivered rifampicin in controlling experimental infection of prosthetic materials.
Method: Under general anaesthesia the carotid sheaths of six sheep were contaminated with 10^7 colony-forming units *Staphylococcus epidermidis*. Six hours later strips of sterile collagen (dry weight 0·5 g) were soaked in 1 ml of a 10 mg/ml solution of rifampicin. One strip was placed into each wound alongside sections of sterile Dacron and PTFE. Blood samples were taken up to 5 days after surgery (to measure rifampicin levels by means of a bacteriological inhibition assay) and wounds were re-explored at day 5 and day 14.
Results: Systemic levels of rifampicin were detected up until 24 h post-implantation with maximal systemic levels (mean 0·35 µg/ml) recorded between 6 and 12 h post-implantation. At day 5 wounds and graft material were bacteriologically sterile in 5 of 6 animals. At day 14, all wounds were sterile. Collagen removed at day 5 had detectable levels of rifampicin, but this was not present at day 14.
Conclusion: This method of drug delivery may be of value in surgical practice to allow a rapid and cost-effective method of providing local antibiotic delivery which also permits delivery of significant levels of systemic antibiotic.

Vascular 039

Popliteal artery entrapment syndrome: a collaborative experience

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Background: Popliteal artery entrapment syndrome (PAES) is a rare condition that is probably under diagnosed. An extensive collective experience has been analysed to show the characteristics of presentation, together with preferred methods of investigation and management.
Method: Cases were collected from members of the Joint Vascular Research Group (10 centres comprise a population of approximately four million) during 1984–1995. Case notes were reviewed in detail.
Results: Twenty-one legs in seventeen patients were affected by the condition. There were fifteen men and two women. The mean age at presentation was 29 years (14–45 years). In one patient, no further information was available and this was therefore excluded from further analysis. The condition was bilateral in four patients in whom three legs were asymptomatic. At presentation, the duration of symptoms ranged from a few hours (acute leg ischaemia) to intermittent claudication of 6 years duration. Primary investigation included angiography (20), duplex (4), plain radiography (1) and MRI (1). There were two cases where thrombolysis was tried initially but failed. Seventeen legs had surgery and the primary procedures were as follows: popliteal artery release (PAR) alone (4), PAR together with thromboendarterectomy and vein patch (4), PAR together with vein patch (2), interposition vein graft (2), femoro-popliteal bypass (4) and thromboendarterectomy and excision of bony exotosis (1). There were two failed primary operative procedures; one femoropopliteal bypass and one interposition vein graft. No surgery was undertaken in three legs. In two of these, the popliteal artery was occluded but gave rise to minimal symptoms. In one case, the popliteal artery was patent and asymptomatic. No legs required amputation. Following surgery, 12 legs were asymptomatic and five had residual symptoms. Three legs have been lost to follow-up.
Conclusion: A diagnosis of PAES should be excluded in young patients presenting with intermittent calf claudication or acute limb ischaemia in the absence of trauma. Although in this series angiography was the most common investigation used to diagnose PAES, MRI has superseded this as it gives excellent anatomical definition of the structures within the popliteal fossa.

Vascular 040

Cyanoacrylate glue improves haemostasis of PTFE vascular anastomoses: a randomized prospective trial

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Background: This study aimed to determine if butyl-2 cyanoacrylate glue (Indermil$^{\text{TM}}$, Loctite Ltd. Dublin) can improve haemostasis of polytetrafluoroethylene (PTFE) vascular anastomoses by reducing stitch-hole bleeding.
Method: Twenty-three patients (7 men, 16 women, mean age 74 years) undergoing PTFE bypass from or to the common femoral artery (CFA) using 5/0 monofilament suture material were randomized to receive glue or no glue. The glue was applied as a sealant along the suture line at completion of the anastomosis to the CFA. On release of clamps, blood loss from the anastomoses and time to absolute haemostasis was measured.
Results: Two patients (both randomized to the glue group) were excluded due to technical defects in the anastomosis requiring additional sutures. The results were as follows:

	Mean blood loss (range)	Mean time to haemostasis (range)
No glue ($n = 11$)	169 ml (5–505 ml)	15 min 4 s (0–65 min)
Glue ($n = 10$)	12 ml (0–42 ml)	2 min 37 s (0–6 min 49 s)

Blood loss and haemostasis time were significantly less with glue ($P < 0{\cdot}01$, Mann–Whitney U-test).

Conclusion: Cyanoacrylate glue is a simple and inexpensive means of improving haemostasis of PTFE vascular anastomoses but does not compensate for technical imperfection.

Coloproctology 010

The outcome of surgical treatments for perineal sinus after proctectomy for Crohn's disease

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Background: The aim of this study was to assess the outcome of surgical treatments for perineal sinus after proctectomy for Crohn's disease.

Method: The medical records of 14 patients who developed perineal sinus after proctectomy for Crohn's disease were reviewed.

Results: There were nine males and five females. The mean age was 33 (range 20–73) years. Perineal sinus occurred in 14 of 54 patients having proctectomy (26 per cent). So far 44 surgical attempts have been made to cure the sinus in these 14 patients: drainage alone (20), radical excision (20), gracilis transposition (2), rectus abdominis flap (2). The mean number of operations is three (±2) and total hospital stay per procedure is 18 (±26) days. In only three patients, the sinus has been resolved by radical excision and closure of the sinus after a mean follow-up of 45 (range 3–135) months. Gracilis transposition and rectus abdominis flap were not successful.

Conclusion: These data question the role of aggressive surgery for perineal sinus in Crohn's disease.

Coloproctology 011

Day surgery coloproctology: what do patients think?

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Background: Increasing numbers of surgical procedures are performed on a day-case basis but colorectal surgical practice has been slow to embrace the concept due to perceived problems with postoperative pain management. The purpose of this study was to assess the reaction of patients to a newly instituted day surgery list dedicated to coloproctology.

Method: Over 1 year, 132 consecutive patients undergoing day-case general anaesthetic colorectal procedures were asked to complete a questionnaire on the first evening and 5 days after surgery. Minor and some intermediate procedures, including haemorrhoidectomy were performed as a daycase. All patients were discharged within 6 hours of operation.

Results: Questionnaires were completed by 105 patients (80 per cent), mean age = 44 (range 16–76) years, male:female = 58:47. Procedures performed were: haemorrhoidectomy (29), lateral sphincterotomy (17), fistula in ano (13), EUA ± biopsy (14), skin tags/warts (9), polyps (9), pilonidal sinus (8), mucosal prolapse (6). Pain scores diminished steadily over the 5 postoperative days. Seventy-six per cent felt postoperative pain was less than or the same as they had expected but 8 per cent thought it would have been reduced if they had stayed in hospital. Eighty-eight per cent had had a bowel action within 2 days. Eighteen per cent contacted their GP within 72 h, mainly because of bleeding, but only half of these required a visit. There were no readmissions. Ninety-two per cent felt they had received the right amount of information before surgery and 86 per cent were satisfied with information given afterwards. Only 11 per cent felt it would be more convenient to stay in hospital for 1–2 nights and 90 per cent would prefer a day-case procedure in the future.

Conclusion: Day surgery coloproctology can be performed safely with minimal impact on primary healthcare services. With appropriate explanation, day-case coloproctology has a high degree of patient acceptance.

Coloproctology 012

Colonic anastomoses: the price of failure

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Background: This study aimed to investigate the mode of presentation and management of anastomotic failure following colonic anastomoses, to identify risk factors predisposing to this complication and to estimate the resultant resource implications.

Method: Anastomotic leaks occurred in 33 of 716 patients undergoing colonic anastomoses over a 6-year period (4·6 per cent) by computer search of all case records of patients admitted to the unit. A case control study was undertaken matching each index case with three controls (non-leak) by type and date of operation. Patients were deliberately not matched for age and sex to permit analysis of these variables.

Results: The median time of presentation of anastomotic failure was 7 days, however, classical symptoms of peritonitis, leukocytosis and pyrexia were absent in 40 per cent of patients. Operative management was required in 24 patients (18 immediate, six delayed) and nine were treated conservatively. Seventy-nine per cent of leaks occurred in patients undergoing left-sided colonic anastomoses. In these patients technical factors associated with anastomotic leaks included cross stapling of the rectal stump ($\chi^2=4{\cdot}23$, $P<0{\cdot}05$), and failure to use pelvic drains ($\chi^2=9{\cdot}7$, $P<0{\cdot}01$) or tetracycline lavage ($\chi^2=10{\cdot}5$, $P<0{\cdot}01$). Mortality was 39 per cent in patients with anastomotic leaks (3·1 per cent in case controls $\chi^2=29{\cdot}5$, $P<0{\cdot}001$). Of the survivors 8/20 were left with a permanent stoma ($\chi^2=32{\cdot}3$, $P<0{\cdot}001$ vs case controls) and 6/14 who had cancer developed local recurrence within 6 months ($\chi^2=7{\cdot}2$, $P<0{\cdot}01$ vs case controls). Patients who developed anastomotic leaks had a total median hospital stay of 36 days of which 4 were spent in ITU, required a median of 12 days of parenteral nutrition and had an estimated total cost of four times that of case controls ($P<0{\cdot}001$ Mann–Whitney U-test).

Conclusion: In this study technical factors associated with anastomotic failure included the use of cross stapling of the rectal stump and failure to use tetracycline lavage or pelvic drains. There are major resource implications arising from failure of colonic anastomoses and further research is required into the prediction of patients likely to develop leaks and into the understanding of the pathophysiology of anastomotic failure.

Coloproctology 013

A prospective trial of unstimulated graciloplasty in traumatic faecal incontinence

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Background: Faecal incontinence due to trauma can often be improved by direct sphincter repair, but if the sphincter defect is large or associated with pudendal neuropathy results are poor. We studied the effect of treating such cases with an (unstimulated) gracilis neosphincter with a view to later electrical stimulation if function was suboptimal.

Method: In a prospective trial 12 patients with intractable faecal incontinence of obstetric ($n=9$) or traumatic ($n=3$) aetiology underwent unstimulated gracilis neosphincter formation combined with simultaneous direct sphincter repair in nine. All had endosonographic sphincter defects greater than one third of the anal circumference, six had a bilateral neuropathy and previous sphincter repairs had failed in four. Patients were taught knee squeeze exercises to augment gracilis contraction and were evaluated with microballoon manometry and symptom questionnaires including Cleveland continence scores.

Results: At a median of seven (range 2–18) months after stoma closure, four patients report excellent bowel function (continence score <6/20). Six had moderate improvements of whom one was further helped by subsequent implantation of a neural electrical stimulator. Three encountered evacuatory difficulties precluding electrostimulation. Perineal sepsis prevented stoma reversal in two.

	Median continence score (range)	Median resting pressure (range)	Median squeeze pressure (range)
Pre-gracilis	18 (14–20)	30 (15–70) cmH$_2$O	46 (30–100) cmH$_2$O
Post-gracilis	13 (2–20)	40 (10–70) cmH$_2$O	60 (20–100) cmH$_2$O
Significance (Wilcoxon)	0·012	0·07 (NS)	0·04

Conclusions: The unstimulated gracilis neosphincter can restore continence when direct repairs alone are likely to fail. Later electrostimulation can further improve those with moderate function provided there is no significant evacuatory difficulty.

Coloproctology 014

Colonic lesions demonstrated by magnetic resonance imaging using intraluminal gadolinium contrast

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Background: Interventional magnetic resonance (MR) machines now allow image-guided colorectal surgery. The aim of this study was to develop imaging techniques for the human colon which are able to detect intraluminal pathology and visualize lymph nodes as a preliminary procedure to MR-guided surgery.
Method: Seven resected colon specimens were studied in a 0·5 T General Electric Signa SP10 Interventional MR machine. There were four right hemicolectomy, one sigmoid and one rectal specimen from segmental resections for carcinoma. There was one specimen from a subtotal colectomy for Crohn's colitis with macroscopic pseudopolyposis. Static imaging [T1/T2 fast spin echo (FSE) and fast gradient recalled (FSPGR), acquisition times 6–90 s] was performed in the head coil in all three orthogonal planes. This was repeated after filling the colonic lumen with a solution of 1 per cent Gadolinium-DTPA (Gd) in water. All specimens were examined in routine histological fashion. Images were interpreted by a radiologist unaware of the histology result and an estimate made of the depth of penetration of the tumours through the colonic wall.
Results: Imaging without intraluminal contrast demonstrated the tumour as a localized thickening of the colonic wall in all six cases but gave little definition of the intraluminal part of the lesion. The wall of the Crohn's colon was clearly abnormally thickened. However, intraluminal contrast delineated clearly the tumours and also identified correctly two further adenomas in one specimen. Pseudopolyps were demonstrated in the Crohn's bowel. Coronal images yielded the greatest information. Mesenteric lymph nodes were easily seen in all specimens. Penetration of tumour into subserosal fat was demonstrated in three cases and a deposit in the extraperitoneal fat in one. These findings were in accordance with those from a histological examination.
Conclusion: MR imaging of the colon using a Gd solution clearly demonstrates space occupying lesions *in vitro*, with scan times short enough to be potentially used *in vivo* and also appears accurate enough to predict depth of invasion through the bowel wall. Further assessment of the technique *in vivo* may now be performed.

Coloproctology 015

Video-rigid sigmoidoscopy versus conventional sigmoidoscopy: a controlled randomized study

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Background: This study aimed to assess the efficacy of a novel fine-bore video-rigid sigmoidoscope (VRS) and compare examination length and patient discomfort to conventional rigid sigmoidoscopy (CRS).
Method: The VRS is connected to a monitor and provides video magnified images of the rectum. It is significantly longer than the CRS (30 vs 22 cm) and thinner (10 vs 20 mm). Air can be insufflated by hand through the tip of the scope and the lens is kept clean by a dedicated wash channel. Fifty-eight patients attending a rectal outpatient clinic were enrolled for the study and all were examined with both the CRS and VRS in a random order. The examinations were performed by one of three surgeons with a colorectal nurse practitioner. Length of insertion and visual analogue discomfort scores were recorded by the person performing the examination. The VRS examinations were recorded on video or still pictures for documentation in the notes. Significant pathology was referred for full colonoscopy where appropriate. Ethical approval was obtained for the study.
Results:

Results (mean = SD)	Pain scores (visual analogue)	Examination distance (cm from anal verge)
Video sigmoidoscope	3·0 = 1·8*	23·2 = 5·9*
Conventional sigmoidoscope	5·5 = 2·7*	16·5 = 3·8*

Wilcoxon signed rank test: *$P<0{\cdot}001$.

Conclusion: The VRS was associated with a significant reduction in patient discomfort and a more thorough examination of the rectum and rectosigmoid. The quality of visualization obtained by the VRS was subjectively far superior, and in addition the examination could be recorded for permanent documentation.

Coloproctology 016

Early detection of colorectal cancer using fluorescence

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Background: Delta-aminolaevulinic acid (5-ALA) is metabolized to the fluorescent photosensitizer protoporphyrin IX (PpIX), which accumulates in tumour tissues, and thus can be used to enhance early detection of cancer and dysplasia by tumour-specific fluorescence. Fluorescence diagnosis (FD) may have potential to enhance endoscopic detection of precancerous and malignant lesions in the colon, e.g. polyps, ulcerative colitis and familial adenomatous polyposis, but has not previously been evaluated in the lower gastrointestinal tract. Therefore, the aim of this study was to evaluate fluorescence patterns in colorectal carcinomas after oral ALA administration to determine whether FD can be applied to the lower gastrointestinal tract.
Method: Fifteen patients with histologically confirmed colorectal carcinoma (8 rectal, 3 right colon, 1 transverse colon, 3 left colon) received an oral dose of ALA (20 or 40 mg/kg) 4–6 h before surgery. Colonic/rectal specimens were evaluated immediately after resection. Tumour PpIX fluorescence was induced by exposure to blue light (380–410 nm), and all fluorescent areas within resection specimens biopsied and correlated with tissue histology (gold standard). Normal colonic and rectal mucosa adjacent to the macroscopic tumour was also exposed to blue light, and fluorescent areas biopsied (controls).
Results: Spectroscopic analysis of the tumour fluorescence confirmed tissue conversion of ALA to PpIX, with spectral emission peaks identified at 630, 680 and 710 nm. Sixty-two biopsies were obtained from fluorescent and non-fluorescent mucosa (macroscopic normal $n=33$, macroscopic abnormal (cancer) $n=29$). All non-fluorescent macroscopic normal areas had confirmed benign histology ($n=33$; 100 per cent), whereas 24/29 (83 per cent) fluorescent areas contained histology confirmed invasive adenocarcinoma. Based on this small study, the sensitivity and specificity of FD for predicting invasive colonic cancer were 83 per cent and 100 per cent, respectively. No adverse side-effects were documented at this dose of ALA, other than a transient elevation of liver transaminases (48 h).
Conclusion: ALA-induced tissue fluorescence can discriminate between normal mucosa and neoplastic colorectal lesions when studied *ex vivo*. This preliminary study suggests that ALA-induced FD has a potential role for endoscopic surveillance of patients at high risk of developing colorectal cancer.

Coloproctology 017

Analysis of 10 000 colonoscopies at a district general hospital with a dedicated endoscopy service

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Background: The Endoscopy Section Committee of the British Society of Gastroenterology (1987) presented guidelines for colonoscopy services, suggesting that 161 colonoscopies per 100 000 population per year should be the minimum ideal provision. We present data derived from 7 years' experience of a dedicated endoscopy unit, of a district general hospital, serving a population of 400 000.
Method: Data were derived from a computer database (Medical Systems Limited) of all endoscopic investigations performed between 1990 and 1996.
Results: A total of 10 165 colonoscopies were performed. The annual number performed each year increased over the 7 years from 1048 in 1990 to 1964 in 1996, representing 500 per 100 000 population. The indications for endoscopy were diagnostic (72 per cent), polyp follow-up (10 per cent), cancer follow-up (5 per cent), inflammatory bowel disease surveillance (6 per cent), haemoccult positive (4 per cent), and family history surveillance (2 per cent). Of the colonoscopies performed, 1422 demonstrated polyps and 541 demonstrated cancers. Over the 7 years the diagnosis of polyps increased by 82 per cent, and that of cancers by 32 per cent. The percentage of normal colonoscopies remained stable over the period. Of the colonoscopies performed for the indication of polyp follow-up, 352 (35 per cent) demonstrated polyps, 19 (2 per cent) demonstrated cancers; of cancer follow-ups, 117 (21 per cent) demonstrated polyps, 24 (4 per cent) demonstrated cancers; of positive haemoccult tests, 80 (21 per cent) demonstrated polyps, 28 (7 per cent) demonstrated cancer; and of family histories, 26 (11 per cent) demonstrated polyps, and three (1 per cent) demonstrated cancer.
Conclusion: The increase in diagnosis of polyps and cancers over the period of study, associated with a stable rate of normal colonoscopies clearly demonstrates that the increase in number of colonoscopies performed is warranted; the significant number of positive findings from the follow-up and screening groups supports the inclusion of these indications in a department protocol. Careful consideration of duration of follow-up and follow-up interval is needed in order to avoid excessive investigation; in our series, the significant number of positive findings in those followed-up three and four times during the period of 7 years suggests that more frequent follow-up in a selected group of patients may be appropriate.

Coloproctology 018

Day case haemorrhoidectomy

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Background: Day-case haemorrhoidectomy is commonplace in many parts of the world but is not available at most hospitals in the UK. We have investigated the uptake and outcome of day-case haemorrhoidectomy in the first 2 years of providing the service at this hospital.
Method: Case-note review with completition of a standard proforma for all patients undergoing haemorrhoidectomy as a day case (same day admission and discharge) or as an in-patient over a 2-year period.
Results: Twenty-seven patients underwent successful day-case closed haemorrhoidectomy while 42 patients were treated as in-patients. One patient required emergency admission for faecal impaction after same-day discharge and one patient had a reactionary haemorrhage. None suffered acute urinary retention. Concomitant medical disease was the reason for exclusion from day-case haemorrhoidectomy in the majority of in-patients treated. Over 70 per cent of in-patients did not require postoperative opiate analgesia.
Conclusion: Closed haemorrhoidectomy with same-day discharge should be offered to all patients who require surgical treatment of haemorrhoids and do not have contra-indications to day surgery.

H&P 010

A pilot study of total enteral and parenteral nutritional support in patients with predicted severe acute pancreatitis

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Background: The aim of this study was to assess the safety of routine early total enteral nutritional (TEN) support in patients with severe acute pancreatitis (SAP). The efficacy of TEN on clinical, functional and psychological outcome variables was also studied.
Methods: Patients with SAP (APACHE II score ≥6 on admission) were randomized to receive total parenteral nutrition (TPN) ($n=8$) or TEN ($n=7$) on admission. Data relating to hospital stay, complications, and time to flatus and stool were recorded. Respiratory function was measured by vitalography and spirometry, muscle function by dynamometry, body fat by dual energy x-ray absorptiometry (DEXA), psychological state with the Hospital Anxiety and Depression scale and fatigue was measured using a visual analogue scale.
Results:

Variable	Feed	Admission	Day 3	Day 7
FEV_1 (L/s)	TPN	1·45 ± 0·45	1·33 ± 0·95	1·89 ± 1·26
	TEN	1·45 ± 0·46	1·64 ± 0·54	2·38 ± 0·50
PEFR (L/min)	TPN	273 ± 138	234 ± 167	331 ± 218
	TEN	330 ± 154	343 ± 101	445 ± 164
Grip (kg)	TPN	9 ± 4	12 ± 4	6 ± 5
	TEN	5 ± 4	5 ± 3	4 ± 4
Fat (DEXA-kg)	TPN	30 ± 13		32 ± 12
	TEN	25 ± 13		29 ± 10
Depression	TPN	9 ± 4	12 ± 4	6 ± 5
	TEN	5 ± 4	5 ± 3	4 ± 4
Fatigue (cm)	TPN	8 ± 1	8 ± 1	4 ± 2
	TEN	8 ± 1	4 ± 1	3 ± 2

All results are mean ± SD.

Patients were of similar age, APACHE II score and body mass index on entry to the study. None of the measured variables was statistically significantly different in the two groups on any of the study days although the TEN patients passed flatus more quickly (day 1 versus 4, $P = 0·04$).
Conclusion: This study has shown for the first time that TEN is safe and as efficacious as TPN in SAP.

H&P 011

Surgical treatment of non-functioning neuroendocrine tumours of the pancreas

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Background: Approximately half the islet cell tumours of the pancreas fail to produce any biochemical 'syndrome'. The clinical and immunohistochemical features of these non-functioning neuroendocrine tumours are reviewed in a large personal series.
Method: Between 1982 and 1997, 51 patients (26 men, 25 women), median age 45 (range 15–76) years, were treated for a non-functioning neuroendocrine tumour. Patients presented with abdominal pain ($n=28$), obstructive jaundice (20), acute/chronic pancreatitis (17), weight loss (14), abdominal mass (13) and severe haemorrhage (8), while three asymptomatic tumours were diagnosed by ultrasound screening; two patients had multiple endocrine neoplasia type 1.
Results: Gut hormone profiles were normal except for four patients with raised serum levels of pancreatic polypeptide. Contrast-enhanced computed tomography and visceral angiography localized the tumour in 44 of 47 patients investigated, and all but five were highly vascular. Surgical treatment comprised 'curative' resection ($n=22$), palliative resection (16), bypass procedures (9) and biopsy alone (4). There were three postoperative deaths and 11 early complications. Of 36 tumours submitted to detailed immunostaining, 35 had more than two general neuroendocrine markers and 28 were clearly positive for one or more gut peptides. Actuarial cumulative survival (Kaplan–Meier product-limit method) was 57·4 ± 7·4 per cent (SE) at 5 years and 45·1 ± 9·8 per cent at 10 years. Patients undergoing curative resection had a survival advantage over those managed palliatively (70·3 ± 10·3 per cent vs 46·6 ± 10·1 per cent: $P=0·04$, log rank test).
Conclusion: Resection of these large hypervascular tumours can be a demanding technical exercise. Even with locally advanced disease, however, it offers an early survival advantage and may preclude an agonal bleed.

H&P 012

Rare pancreatic tumours

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Background: This study aimed to review the presentation, operative course and progress of 98 patients with a rare pancreatic tumour who underwent surgery between 1977 and 1997. 'Rare' was defined as tumours that were not typical ductal or ampullary adenocarcinomas.
Method: The records of the patients were collected prospectively and follow-up was undertaken in a dedicated pancreatic clinic or by telephone by a specialist nurse. Data on presentation, operation, postoperative stay, complications and survival were recorded. The pathology was undertaken by a pathologist with an interest in pancreatic disease.
Results: Twenty-three patients presented with endocrine symptoms (insulinoma 22, gastrinoma 1); these patients had their tumour removed without mortality and all are alive or died without recurrence. Seventy-five patients presented either for diagnosis of pancreatic symptoms, on account of a very large mass, or as a differential diagnosis of a ductal carcinoma. These 75 tumours were treated by pancreatoduodenectomy ($n=38$), distal resection ($n=32$) and local excision ($n=5$). Three postoperative deaths occurred due to sepsis and haemorrhage (day 51), a pancreatic anastomotic leak and sepsis (day 47), and respiratory failure (day 25). The median length of stay was 12 days (range 7–42), and 25 patients had complications, two of whom required reoperation. The final histology was varied [neuroendocrine (29), cystadenoma (17), cystadenocarcinoma (7), mucin hypersecreting intraductal (7), hamartoma (3), hypernephroma (2), and 10 further miscellaneous malignant tumours]. At a median of 45 [range 1–240] months follow-up, 10/70 patients had died of recurrent disease (5/29 neuroendocrine, 2/2 hypernephroma and 3/8 miscellaneous malignant tumours).
Conclusion: The importance of identifying and treating these lesions is emphasized on account of their improved prognosis. Some of the larger tumours present a formidable technical operative undertaking, but the morbidity and mortality of the operation with its good outlook justifies the procedure.

H&P 013

The correlation between spiral computerized tomography (CT), endoscopic ultrasound and surgery in pancreatic and ampullary tumours

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Background: The aim of this study was to examine the correlation between findings on spiral computerized tomography (CT) and endoscopic ultrasound (EUS) and surgery.

Method: Thirty-eight patients with pancreatic or ampullary tumours had spiral CT and EUS performed. Twenty-one were explored surgically with a view to resection. Findings from spiral CT and EUS were compared to findings at laparotomy.

Results: Seventeen of the 38 patients had very advanced disease or were unfit for surgery. Of 21 patients who had a laparotomy (17 pancreatic, four ampullary carcinoma) eight had resections and 13 had palliative bypasses performed. The tumour was identified by spiral CT in 67 per cent and EUS in 95 per cent of cases. Spiral CT failed to demonstrate five of the eight resectable tumours. EUS identified all of these.

	EUS sensitivity (%)	EUS specificity (%)	Spiral CT sensitivity (%)	Spiral CT specificity (%)
SMV/PV involvement	81	71	55	100
SMA involvement	25	100	50	100
LN metastasis	46	100	33	100

SMV/PV = superior mesenteric and portal vein; SMA = superior mesenteric artery; LN = lymph node.

Conclusion: EUS is better than spiral CT in demonstrating small, potentially resectable pancreatic and ampullary lesions. EUS is better than spiral CT in detecting SMV/PV involvement but the SMA is better evaluated by spiral CT. EUS may be more sensitive at demonstrating lymph node metastases.

H & P 014

Management of non-parasitic hepatic cysts: an evolving picture

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Background: There is considerable debate as to the most effective management of symptomatic non-parasitic liver cysts. The aim of this study was to assess the evolution of surgical management with the advent of laparoscopic treatment, and to determine outcome for patients with simple cysts and adult polycystic liver disease (APLD).

Method: All patients surgically treated for liver cysts over a 9-year period were identified and case notes reviewed retrospectively to ascertain presenting symptoms and signs, investigations, surgical management and outcome. Simple cysts were defined as a single dominant cyst (± occasional small adjacent cysts) while polycystic lesions consisted of extensive multiple bilobar cysts. The latest patient contact was either in the clinic or via a telephone interview.

Results: Thirty-eight patients underwent 48 operations during the study period with a mean follow-up of 40 months. Twenty-three cases had simple cysts and 15 APLD, with seven (47 per cent) of the APLD patients having associated renal cysts. There was a marked female predominance, with over 90 per cent in each group. The simple cyst patients were older (mean age 62 years, range 33–84 years), compared to the APLD cases (51 years, range 39–79 years). All major symptoms were pressure related and included pain, fullness and nausea. The mean simple cyst diameter was 14·3 cm. Of the three surgical approaches employed (laparoscopic deroofing (20), open fenestration (14) and hepatic resection (14), the mean operation times were 94, 95 and 192 minutes, respectively with a mean postoperative stay of 3·5, 9 and 12 days. Seven of 14 hepatic resections required intraoperative blood transfusion. There was no mortality but postoperative morbidity included ascitic and bile leakage in addition to recognized postoperative complications. Twenty-three cases with simple cysts underwent a total of 26 operations. The laparoscopic group had a re-intervention rate of 8 per cent (1/13) compared to 29 per cent (2/7) for the open group. After hepatic resection no patient required re-operation. For the polycystic cases laparoscopic surgery was less successful with 5/7 (71 per cent) requiring re-operation, with one patient undergoing two subsequent operative procedures.

Conclusion: Laparoscopic deroofing has a potential role in the management of liver cysts in carefully selected cases but with a high re-intervention rate noted in polycystic disease, with posterior and central cysts accounting for most of the failures. An aggressive management approach appears justified in the management of symptomatic cysts to avoid further operative episodes but the overall outcome in APLD is less satisfactory.

H & P 015

An eicosapentaenoic acid-enriched nutritional supplement reverses cachexia in patients with advanced pancreatic cancer

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Background: Conventional nutritional supplements do not affect the progress of cachexia in patients with advanced cancer. This study attempted to ascertain whether a nutritional supplement enriched with EPA could affect cachexia in patients with pancreatic cancer.

Method: Twenty patients with unresectable pancreatic cancer were asked to consume two cans of an EPA-enriched nutritional supplement daily in addition to their normal food intake. Each can contained 310 kcal, 16·1 g protein and 1·09 g EPA. Weight, body composition, dietary intake and resting energy expenditure (REE) were measured at baseline and after 3 weeks. Weight and body composition were measured monthly thereafter.

Results: Two patients experienced worsening or development of steatorrhoea. Otherwise no intervention-related adverse events were seen. Patients consumed a median of 1·9 cans/day. All patients were losing weight at baseline at a median rate of 3·3 kg/month (interquartile range 4·8–1·9). After administration of the EPA-enriched supplement patients had significant weight-gain at 3 (median 1 kg (range 0–2), $P = 0{\cdot}01$) and 7 weeks (median 2·5 kg (range 0·1–5·8), $P = 0{\cdot}03$). There was no change in percentage total body water suggesting weight-gain was not due to the accummulation of water. Analysis of body composition revealed a significant gain in lean body mass ($P = 0{\cdot}03$) and no change in fat mass after 3 weeks. Dietary intake increased from a median of 1319 kcal/day to 1635 kcal/day ($P = 0{\cdot}04$) and REE/kg lean body mass fell significantly ($P = 0{\cdot}02$).

Conclusions: In contrast to previous studies of conventional nutritional supplements in cancer patients losing weight, this study suggests that an EPA-enriched supplement may reverse cachexia in advanced pancreatic cancer. A randomized, placebo-controlled trial of this supplement is planned.

H & P 016

Judicious use of biliary stents in patients with difficult common bile duct stones is safe and effective

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Background: The removal of common bile duct (CBD) stones difficult and associated with a morbidity rate of 10–15 per cent with mortality rates of 2–5 per cent. Biliary endoprosthesis are a simple, safe and effective method of treating patients with difficult CBD stones and this study reports our experience.

Method: Stents were inserted at endoscopic retrograde cholangiopancreatography (ERCP) in the following clinical situations: patients with jaundice or cholangitis in whom the duct was not cleared at the first attempt, unremovable large or impacted stones and the elderly, frail or uncooperative patient. The stent helped in the resolution of the acute crisis and allowed planning of subsequent strategy. There were three patient subgroups following stent insertion and they are: Group 1: long-term stent group; Group 2: staged endoscopic stone removal; and Group 3: open stone retrieval.

Results: Between November 1992 and July 1997, 70 patients with difficult CBD stones were stented as per the above criteria. All patients had prophylactic antibiotics and no patient had a coagulopathy. The study group comprised 25 men and 45 women, the median age was 78 (range 21–93 years). Seventy per cent of patients were >70 years and 43 per cent >80 years. In addition to age, 40 per cent had other significant co-morbidity. Attempted stent insertion was successful in every patient. These 70 patients underwent 161 ERCPs, 86 of which involved sphincterotomies. The results of treatment are shown below:

Treatment group	No. patients (%)	Median age	Co-morbidity	Morbidity	Mortality
1	20 (28·5%)	84·5	55%	1	1
2	42 (60·0%)	75·0	52%	4	0
3	8 (11·5%)	63·5	37%	1	0

The overall morbidity was 8·5 per cent, i.e. cholangitis = 4, bleeding = 1 requiring OGD and injection, pancreatitis = 1. One patient died (1·4 per cent) of sepsis 25 days poststent insertion. The mean follow-up was 28 (range 2–60) months and nine patients have died of unrelated causes.

Conclusion: We believe that insertion of an endoprosthesis at ERCP is a simple method of dealing with a difficult problem and our results show much lower incidence of complications and mortality than previously reported.

H&P 017

Normal HBA1C after pancreatic islet autotransplantation

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Background: Pancreatic islet autotransplantation (AT) combined with total pancreatectomy for chronic pancreatitis (CP) can prevent insulin independence, but not in all cases, a proportion of patients still require exogenous insulin. The aim of this study was to assess insulin secretion after a glucose challenge and general diabetic control in those patients with a functioning islet auto-graft.

Method: All patients received a 75 g oral glucose tolerance test. AT patients were compared to patients with CP either with normal ($n=15$) or impaired ($n=6$) glucose tolerance and non-diabetic patients (controls) without CP. In addition, HBA1C levels were also assessed but only in AT recipients and those having total pancreatectomy and those without an AT ($n=8$).

Results:

	C-Pep (pmol^{-1})	Glucose (0 min)* mmol^{-1}	Glucose (2 h) mmol^{-1}	Insulin (30 min) pmol^{-1}
Controls	663	3·5–5·5	<7·8	304
CP (normal GTT) $n=15$	663	4·3	4·5	387
CP (impaired GTT) $n=6$	467	7·1	10·7	101
AT $n=11$	444	7·9	17·5	144

*Fasting samples. All mean values.

Conclusion: Despite fasting, and 2 h hyperglycaemia with a reduced stimulated insulin response after a glucose challenge, AT recipients have significantly better glucose control as HbA1c levels were in the normal range (95 per cent c.i. 5–7·5) when compared to those patients having a total pancreatectomy without AT (955 c.i. 8·5–11·5). This suggests that *in vivo* insulin secretion, though not enough to achieve total insulin independence, is better than exogenous insulin therapy alone, in terms of achieving near normoglycaemia.

H&P 018

Is local and intraperitoneal instillation of bupivacaine after laparoscopic cholecystectomy effective for pain?

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Background: In a prospective study we have tried to determine whether the use of bupivacaine is beneficial for pain relief following laparoscopic cholecystectomy. We have also tried to compare different methods of administration.

Method: Patients were randomized into four groups. Three treatment groups and one control. Treatment groups received 40 ml of 0·25 per cent bupivacaine. Group I was given bupivacaine by peri-portal infiltration, Group II by intra-peritoneal instillation, Group III by peri-portal infiltration (20 ml) and intraperitoneal instillation (20 ml) and Group IV was given 40 ml of normal saline (20 ml locally and 20 ml intraperitoneally). There were 10 patients in each group. All patients had same standard anaesthesia. Visual analogue pain scale was used to assess patients' pain 2, 4 and 24 h after surgery. All patients were given 100 mg of diclofinac suppository. They were also allowed coproxamol and morphine as required.

Results: The mean scores at 2 and 4 h after surgery were lower in all three treatment groups than in the control group although it was not statistically significant. The greatest effect was seen after 24 h after surgery in Group III mean 2·00 versus 4·25, $P<0·05$. Morphine requirements were significantly lower in the treatment group ($P=0·008$). Coproxamol usage was lower but not significant.

Conclusion: The numbers were small but this study does show bupivacaine is a useful adjunct for analgesia and is most efficacious when used in combination of local and intraperitoneal instillation.

Breast 10–24 — *Friday 15 May, 14·00–16·00*

Breast 010

Oestrogen receptor status strongly influences recommendations for adjuvant systemic therapy in higher risk breast cancer patients

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Background: The importance of oestrogen receptor (ER) status has been demonstrated in recent publications but it is still not available in many breast units throughout the UK. The aim of this study was to investigate the role that ER plays in the selection of adjuvant therapy in 100 consecutive patients with primary, operable, invasive breast cancer.

Method: Pathological prognostic indicators and recommended systemic therapy are recorded prospectively in all patients with breast cancer treated at the Western Infirmary. Following a 4-month period the histopathology of 100 consecutive cases was reviewed, including tumour type, size, grade, node status and lympho-vascular invasion but the ER status of each patient was blinded. A consensus plan for systemic therapy was then produced for each patient and compared with the original plan which had been decided on the basis of the above prognostic indicators but included ER status as well.

Results: Despite the absence of ER status it was still possible to predict current optimal adjuvant therapy (compared with the original recommendations) in the following groups: Group 1: >69 years, 18 of 20 patients (90 per cent); Group 2: postmenopausal, T1 N0 up to Grade 2, 14 of 14 patients (100 per cent); Group 3: patients eligible for BASO II study (T1, N0, Grade 1), 11 of 12 patients (92 per cent). In the remaining patients the absence of ER status resulted in inappropriate recommendations for adjuvant systemic therapy in 31 of 54 patients (57 per cent). Lack of ER status also influenced clinical trial accrual and in premenopausal patients contributed to a greater number being offered chemotherapy with no patients being randomized for ovarian ablation.

Conclusion: The availability of ER status strongly influences the prescription of adjuvant systemic therapy in patients with primary operable breast cancer. However, if a selective policy is used, which may be more cost-effective, all premenopausal patients and higher risk postmenopausal patients should have ER status performed.

Breast 011

Prospective assessment of early morbidity following axillary clearance for breast carcinoma

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Background: Axillary clearance is an accepted part of the assessment and management of patients with breast carcinoma, but is associated with morbidity, particularly arm swelling and limitation of shoulder movement. The aim of this study is to prospectively monitor patients for the development of these complications.

Method: We have studied 96 patients all of whom had level 1–3 axillary clearance. Measurements were taken preoperatively and at intervals postoperatively. Arm volume was measured using an optoelectronic volometer (Bosl Medizintechnic). Shoulder movements were measured with a goniometer.

Results:

Arm volume	No. patients	Mean ipsilateral volume (mean change, ml)	Mean contralateral volume (mean change, ml)	Swelling >200 ml (*n*)
Preoperative	96	1532 —	1520 —	0
2 days	93	1505 (−12)	1488 (−13)	0
5 days	92	1498 (−42)	1484 (−41)	0
3 months	37	1596 (+41)	1573 (+14)	3
6 months	40	1620 (+87)	1585 (+62)	3
1 year	15	1571 (+183)	1521 (+157)	1

Over the first postoperative week, the mean volume of both arms fell. No patient developed swelling of greater than 200 ml. Seven patients subsequently developed significant upper limb swelling. Swelling was detected at an early stage, and all were referred for physiotherapy. Two of these patients (28 per cent) had had wound infection compared to 12 per cent of those without swelling. There was no difference in the type of surgery performed, the number of nodes retrieved or the development of seromas between the two groups. Movements were expressed as a percentage of the preoperative values. Abduction, adduction and flection were severely impaired at day 5 after operation (68 per cent, 76 per cent, and 75 per cent, respectively). These had recovered almost fully by 6 months after operation (all >90 per cent of preoperative range). Extension and external rotation were not impaired.

Conclusion: The volometer was found to be a useful means of detecting arm swelling, so allowing early treatment. Shoulder function returns to normal in the majority of patients.

Breast 012

Neural networks are superior to the traditional prognostic indices for breast cancer patients

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Background: An artificial neural network (ANN) is a form of artificial intelligence that is able to learn non-linear causal relationships between data sets and therefore has a theoretical advantage over the traditional linear statistical methods used in the construction of prognostic indices. We therefore compared the ability of ANNs to predict outcome in breast cancer with the established Nottingham prognostic index (NPI).

Method: Data on 460 patients collected retrospectively on the standard BASO database were used to train and validate the ANN. As with the NPI the size, grade and lymph node status were used as the input nodes with a variable number of neurones utilized in the hidden layer and a simple positive/negative output neurone. The ANN was trained to predict death at 1 year on 435 patients and then validated on data from 25 randomly selected patients which had been removed prior to training. The ANNs predictions were then compared to the patients' NPI group.

Result: The ANN achieved an overall accuracy of 84 per cent (95 per cent c.i. 0·70–0·98) for the prediction of death at 1 year. The positive predictive value of the network's predictions was 1·0 and the negative predictive value 0·83. In contrast, of the patients in the same validation set, 38 per cent of patients in the moderate-risk group were dead at 1 year as compared to only 33 per cent of patients in the high-risk group.

Conclusion: Artificial neural networks are able to predict outcome for breast cancer patients with greater accuracy than the traditional prognostic indices and particularly for the majority of patients in the 'moderate' risk group. Furthermore, ANNs can be trained on data available from a standard national database and could therefore be easily incorporated into such a programme in order to facilitate a prospective analysis.

Breast 013

Identification of genetic aberrations in breast tumours

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Background: The aims of this study were to use a novel cytogenetic technique, comparative genomic hybridization (CGH) to study genetic aberrations in breast cancer. CGH allows analysis of the entire genome for chromosomal deletions or amplifications in a single hybridization.
Method: CGH is based on the competitive hybridization of two differentially labelled DNA samples to normal metaphase spreads. Tumour DNA is labelled with a green fluorochrome and normal reference DNA is labelled with a red fluorochrome. Image analysis compares the intensity of the green to red staining and calculates the ratio thus allowing copy number changes to be identified throughout the genome. Twenty consecutive breast tumours were studied. All were staged according to standard TNM classification. Reference DNA was extracted from the patients lymphocytes and in order to distinguish between somatic and germline mutations the tumour specimens were also compared using standard reference DNA.
Results: Recurrent regions of amplification involved 1q (80 per cent), 3q (70 per cent), 5q (55 per cent), 12p (55 per cent) and 20p (70 per cent). The average number of amplifications per tumour was 12·5 ± 6·2, involving 8·2 ± 3·1 chromosomes in each tumour. Recurrent regions of deletion involved 17p (45 per cent) and 15p (45 per cent). The average number of deletions per chromosome was 10 ± 4·1, involving 5·3 ± 3·6 chromosomes in each tumour. The greatest number of aberrations (30) was found in a T4 tumour. The sites of most of the copy number changes were distinct from those of currently known cancer genes.
Conclusion: From this study it can be identified that there is a multigene involvement in breast carcinogenesis and that there are potentially a number of oncogenes or tumour suppressor genes involved in malignant progression which have not yet been identified. This has implications for future studies in breast cancer.

Breast 014

Recurrence of ductal carcinoma *in situ*: is wide local excision as safe as mastectomy?

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Background: Wide local excision (WLE) is increasingly advocated for localized ductal carcinoma *in situ* (DCIS) lesions (<40 mm mammographic diameter) yet many studies show higher recurrence rates following WLE than following mastectomy. To determine the safety of WLE as a procedure for localized DCIS lesions, recurrence rates following WLE or mastectomy were compared.
Method: Clinical, radiological and histopathological data from a consecutive series of 284 women with confirmed DCIS (<40 mm diameter) presenting to one Breast Unit over a period of 23 years (1974–1996) were examined.
Results: Women were treated by WLE (n = 174, 60 per cent) or mastectomy (n = 114, 40 per cent). Incidence of comedo necrosis, microinvasion and high nuclear-grade tumours were similar in both groups of patients. Local relapse was defined as ipsilateral recurrence of *in situ* or invasive ductal carcinoma (see table). Sixty-six (39 per cent) women undergoing WLE have received adjuvant therapy [tamoxifen n = 41 (24 per cent), radiotherapy n = 19 (11 per cent), both tamoxifen and radiotherapy n = 6 (4 per cent)].

	Screen detected cases	Median size of lesion [mm] (range)	Local relapse	No. invasive recurrences
WLE n = 170	146 (86%)	12 (2·5–40)	20 (12%)	2 (10%)
Mastectomy n = 114	46 (40%)*	18 (2–40)*	7 (6%)**	3 (43%)

*P = <0·001, **P = not significant, statistics by χ^2 test.

Multivariate analysis revealed involved margin status to be the only significant predictor of local recurrence following WLE. Local relapse occurred in 13 of 53 (25 per cent) women with uncertain or involved biopsy margins and 7 of 117 (6 per cent) women in whom biopsy margins were clear of DCIS (P = 0·001).
Conclusion: Women with localized DCIS (<40 mm) may safely be offered WLE but it is essential that excision biopsy margins are clear of DCIS. If this criterion is achieved, relapse rates equal those seen following mastectomy.

Breast 015

Neoadjuvant chemotherapy for primary breast cancer: how many breasts are saved?

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Background: Neoadjuvant chemotherapy is advocated in women with large primary breast cancers to improve the chances of breast conservation. The aim of this study was to assess clinical and mammographic response rates following primary chemotherapy for breast cancer, and relate this to mastectomy rates and mammographic predictors of response.
Method: A retrospective review of 95 women (97 tumours) receiving neoadjuvant combination chemotherapy for primary breast cancer was undertaken. The initial mean tumour diameter was 6·5 cm (± 2·1 cm). Ninety-two per cent of women had mammograms at diagnosis. The median postoperative follow-up was 20·5 (range 0–73 months).
Results: Overall, 77 per cent responded to chemotherapy but 52 per cent had a mastectomy. Non-responders had a significantly greater chance of mastectomy than responders (χ^2 = 5·9, P = 0·015). When pre-chemotherapy mammograms showed widespread microcalcification 13 out of 20 (65 per cent) failed to show a mammographic response to therapy ($P \leq 0·01$).

	Complete	Partial	Stable	Progressed
No. patients	29 (32%)	41 (45%)	17 (19%)	4 (4%)
Alive	26	28	11	2
Mastectomy	8 (28%)	23 (56%)	12 (71%)	4 (100%)
No. patients node positive	8 (28%)	22 (54%)	12 (71%)	3 (75%)

Conclusion: Although neoadjuvant chemotherapy obviates the need for mastectomy, the high rate of axillary nodal involvement (even in the complete responders) means that axillary node clearance is required. Widespread mammographic microcalcification (indicative of ductal carcinoma *in situ*) responds poorly to neoadjuvant chemotherapy, and is inappropriate in women who have these mammographic appearances at diagnosis.

Breast 016

Life insurance assessment for familial high risk and proven breast cancer patients

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Background: There is considerable confusion as to the insurability of women with either a high risk of developing breast cancer or who have had a previous diagnosis of breast cancer. The aim of this study was to seek clarification from the insurance industry on these points.
Method: A questionnaire was sent to all life insurance companies in the UK and registered with the ABI (Association of British Insurers). There were eighteen replies which included nine of the top 20 life insurance companies and also the most frequently used reinsurance company which influences 70 per cent of the UK reinsurance business.
Results: For known breast cancer patients 8 to 12 years has to elapse following treatment, before a woman is insurable, significantly axillary lymph node status is an essential component required in their assessment. Patient follow-up is expected and assumed to be conducted by appropriate clinicians. Involvement in clinical trials, which do not follow protocols similar to standard treatment, may affect a woman's ability to obtain life insurance. For high-risk patients, the use of genetic test results depends on the type of insurance required. For sums less than £100 000 the insurance industry has agreed, for the time being, not to use genetic information in their assessment. However, family history remains important and this information still needs to be declared, and for insurance sums greater than £100 000 the assessment is individualized and advice from reinsurance companies is sought. A negative genetic test will usually bring the premium loading back to normal.
Conclusion: Greater debate and discussion between breast cancer clinicians and life insurance companies is needed to allow a better mutual understanding of their practices. The interface between medicine and the insurance industry needs more clarity to ensure life insurance companies are kept well informed of the changes in clinical practice.

Breast 017

The management of patients with intermediate (AC3) cytology and a solitary breast lump: is a conservative approach safe?

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Background: The management of patients with AC3 cytology is controversial but in our unit excision biopsy has been routinely advised. We wished to review our policy to determine if a more conservative policy was safe.
Method: The records of all patients seen in the one-stop breast clinic with a discrete lump, who had a AC3 result on fine needle aspiration cytology (FNAC) over a 3-year period were reviewed. Clinical and mammographic findings at presentation were correlated with histopathological diagnosis.
Results: Between March 1994 and August 1997, 43 patients, median age 46 (range 21–72) years, had an intermediate FNAC result. Thirty-two patients underwent excision biopsy, two refused surgery and in five benign histology was obtained from trucut samples. The other four patients were treated conservatively and further cytology obtained at a later date, which was benign in all cases. Benign histology was obtained in 25 patients, eight patients had an underlying primary invasive breast cancer, two had a phylloides tumour and one had widespread ductal carcinoma *in situ*. All but two of the patients with underlying primary invasive breast cancer had associated abnormalities detected by clinical examination or on imaging. In the remaining two patients there was no clinical or mammographic suspicion of malignancy.
Conclusion: AC3 breast cytology must be taken seriously as it is frequently an indicator of underlying malignancy. The results of this study indicate that definite histology should be obtained in all patients because of the unacceptably high false-negative rate of clinical and radiological assessment in this group.

Breast 018

Impact of guidelines for general practitioners on fine needle aspiration of breast masses

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Background: Recent guidelines indicate that fine needle aspiration (FNA) by GPs is only acceptable in cases with recurrent breast cysts where the GP has the necessary skills. This study was designed to assess changes in GP practice as regards FNA since the introduction of these guidelines in November 1995.
Method: A retrospective review of 70 patients attending the breast clinic between May 1994 and July 1997, whose referral letter stated that they had recently undergone FNA by their GP, was performed. Twelve patients were in the group before guidelines were issued and 58 afterwards.
Results: Twenty-four patients had cysts aspirated by the GP. In the pre-guideline group all four patients had the fluid sent for cytological examination. Two needed further aspiration in clinic. After introduction of the guidelines, only 10 of 20 (50 per cent) had the fluid sent with nine out of 20 (45 per cent) needing further aspiration. Thirteen patients with a final diagnosis of carcinoma had undergone FNA by their GP. In the 1994–5 group all five patients had specimens sent for cytology. None was diagnostic of maligancy but three were suspicious. One was inadequate. In 1996–7, eight patients with malignancy had an FNA by their GP, but the specimen was not sent in six cases. The two sent were suspicious. Nineteen patients with benign breast change and no discrete mass had undergone FNA by their GP. Pre-guidelines there were two cases, both specimens were sent for cytology. Post-guidelines 17 patients had FNA and the specimen was not sent in 10.
Conclusion: Despite the guidelines, cyst fluid is still often sent unnecessarily and FNA is performed inappropriately and inaccurately by GPs.

Breast 019

Letrozole as primary medical therapy for locally advanced and large operable breast cancer

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Background: This study aimed to investigate the efficacy of letrozole given as primary systemic therapy and to compare responses with those obtained with tamoxifen in an identical clinical situation.
Method: Twenty-four patients were treated with letrozole (12 at 2·5 mg, 12 at 10 mg) and 65 patients were treated with tamoxifen. All were at similar stages $T_2 > 3$ cm, T_3, T_{4b}, N_{0-1}, M_0. All tumours were oestrogen-receptor (ER) positive (>20 fmol/mg cytosol protein or histoscore >80). Patients were monitored by monthly ultrasound and the change in volume over a 3-month period was calculated.
Results: The median percentage reduction in tumour volume with letrozole was 81, 95 per cent CI 69–86. Prior to letrozole 15 patients would have required mastectomy but after 3 months of therapy all were suitable for treatment by breast conservation. There was one complete pathological response and three patients had residual microscopic tumour foci only at the time of definitive surgery. In a series of 65 patients treated using an identical protocol with tamoxifen, the median percentage reduction in tumour volume was 48 (95 per cent, CI 27–48). Although not a randomized study this was a much lower reduction than that obtained by letrozole ($P < 0·005$).
Conclusion: Letrozole is highly effective when used as primary systemic therapy for large operable or locally advanced breast cancer and at least as good as tamoxifen in this setting.

Breast 020

Scintimammography in the assessment of local recurrence following conservative breast surgery

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Background: Clinical assessment and mammography are unreliable in detecting local recurrence following conservative surgery for breast carcinoma. This study was designed to evaluate scintimammography (^{99m}Tc-Tetrofosmin) in determining malignancy in patients presenting with palpable masses who had previously undergone segmental mastectomy and radiotherapy for breast carcinoma.
Method: Eleven patients with suspected local recurrence following conservative breast surgery had scintimammography, plain film mammography and magnetic resonance (MR) mammography performed on the same day. The films were graded (benign or malignant) by a blinded radiologist before the lumps were diagnosed as benign or malignant based on histology (excision biopsy) or cytology (fine needle aspiration cytology). Four of the eleven patients (36 per cent) had recurrent breast carcinoma.
Results: ('+' indicates a positive (malignant) and '–' a negative (benign) test result).

		Plain film		MR mammogram		Scintimammogram	
	Histology	+	–	+	–	+	–
Malignant	4	2	2	3	1	4	0
Benign	7	0	5	1	6	0	7

Conventional mammography missed recurrent carcinoma in two patients and suggested recurrence in two others with postoperative fibrosis alone (negative predictive value 71 per cent). MR mammography correctly characterized seven lesions with one false-positive and one false-negative (negative predictive value 86 per cent). However, scintimammography correctly diagnosed all eleven patients (negative predictive value 100 per cent).
Conclusion: Scintimammography is inexpensive, acceptable to patients, uses equipment readily available in most hospitals, and is superior to conventional or MR mammography in the assessment of the previously operated and irradiated breast. We suggest that scintimammography should form part of the routine assessment of these patients.

Breast 021

Higher incidence of contralateral breast cancer in patients with a positive family history

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Background: The identification of breast cancer susceptibility genes has increased the awareness of family history as a risk factor for breast cancer. The effects of a family history on presentation and pathology of breast cancer were the focus of this study.
Method: The records of patients undergoing modified radical mastectomy between 1979 and 1987 were reviewed. All patients with at least one first-degree relative with breast cancer were identified.
Results: A total of 1024 patients were identified, 171 (17 per cent) had a positive family history, there was no family history in 709 (70 per cent) and the status was unknown in 144 (14 per cent). Comparison of the patients with and without a family history showed no differences in mean age at presentation (55 versus 56 years), proportion of patients younger than 40 years (24 of 171 versus 76 of 701), predominant tumour type, multicentricity within the breast (35 of 171 versus 158 of 701) patients with T1 tumours (105 of 171 versus 447 of 701), axillary lymph node involvement (50 of 171 versus 215 of 701), oestrogen receptor status (82 versus 327) progesterone receptor status (40 versus 182). At a median follow-up of 83 months the incidence of contralateral breast cancer was higher in patients with a family history (10 compared to 17, χ^2 test, $P=0.03$). The median time to detection of the contralateral cancer was similar in both groups (43 months).
Conclusion: We conclude that patients with a family history of breast cancer do not have features at presentation or pathology that would merit a change in treatment strategy. However, the risk of contralateral cancer is increased.

Breast 022

Randomized controlled trial of the psychological effectiveness of multimedia computer counselling in symptomatic breast clinics

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Background: More effective information transfer during counselling may help to reduce levels of anxiety in women attending symptomatic breast clinics. Multimedia has several theoretical advantages over the traditional leaflet-based approach and it was therefore decided to compare the psychological effectiveness of these two modalities.
Method: The multimedia counselling system was designed in our unit and evaluated in the clinical situation prior to the commencement of the prospective trial. A prospective randomized trial was then performed with patients from the symptomatic clinics being randomized to receive either traditional counselling or counselling with the multimedia system. The Speilberger State Trait Anxiety Scale was used to record psychological distress prior to the consultation, after being informed of the diagnosis and after counselling. In addition each patient was asked to complete a satisfaction questionnaire based on the Wolf Medical Interview Satisfaction Questionnaire.
Results: To date, 40 patients have been recruited: 18 were randomized to receive traditional counselling and 22 to receive multimedia counselling. There was no statistical difference in the levels of psychological distress between the two groups at any stage. However, a comparison of the satisfaction questionnaire showed that the patients found the counselling provided with the multimedia system superior to that provided by the traditional approach.
Conclusion: These preliminary results demonstrate that multimedia counselling is at least as psychologically effective as the traditional leaflet based approach and is preferred by the majority of patients. However, the advantages conferred by the use of multimedia counselling tools is such that they will undoubtedly become an essential counselling tool for use with patients with symptomatic breast disease.

Breast 023

Axillary sentinel node identification in breast cancer with dye injection alone

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Background: Recent reports have suggested that identification and examination of the axillary 'sentinel' node can accurately determine axillary node status in breast cancer patients. Conventionally both radioisotope enhanced lymphoscintigraphy and peroperative blue dye injection are utilized to identify the sentinel node but this study examines the results of dye injection alone.

Method: Thirty-eight women with proven breast cancer (age range 35–86 years) had 4 ml Isosulfan blue colloid dye injected peritumourally after induction of anaesthesia. The sentinel node was identified as the most proximal node that was blue or the first axillary node encountered by a blue lymphatic and sent for separate histological study. All patients then proceeded to standard axillary dissection.

Results: Of the total of 38 patients, 14 had wide local excision and 24 mastectomy as their associated breast procedure. A total of 718 nodes were retrieved (mean = 19) and 19 axillae contained metastatic disease. A sentinel node was satisfactorily identified in 35 (92 per cent) as a blue node ($n = 18$) or the termination of a blue lymphatic ($n = 17$). There were three false-negative results for axillary nodal status (8 per cent) with overall sensitivity of 84 per cent. Patients treated by wide excision and separate axillary dissection were technically more difficult.

Conclusion: Sentinel node identification is a developing technology and is possible for a majority of patients using dye injection alone. The absolute accuracy and failure rate require further study after the learning curve is completed.

Breast 024

Evidence-based appraisal of the one-stop breast clinic

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Background: The assumption behind a focused one-stop clinic system is that rapid diagnosis and treatment leads to improved patient management. Based on our early experience of a one-stop breast clinic we set about testing this assumption.

Method: Patients with breast cancer diagnosed during a 6-month period of one-stop breast clinic (OSBC) (1/9/96–28/2/97) were retrospectively compared with patients diagnosed from a 6-month period of fast track clinic (FTC) (1/3/96–31/8/96).

Results: Thirty-one patients diagnosed with breast cancer via OSBC were compared with 41 patients diagnosed from FTC. We observed a decrease in the times from: a) referral to diagnosis (mean 3·4 versus 4·9 weeks); and b) referral to definitive surgery (mean 5·8 versus 7·3 weeks). The average number of visits per patient, prior to definitive treatment, in the OSBC was 1·2 compared to 2·0 in the FTC group. Thirty-nine per cent of patients attending the OSBC (12 of 31) versus 46 per cent of FTC patients had a diagnostic cytology (C5 fine needle aspiration). Four patients in each group required core biopsy (12·9 per cent, OSBC versus 9·7 per cent FTC). Forty-eight per cent of patients in the OSBC group (15 of 31) versus 44 per cent of patients in the FTC (18 of 41) required surgery for tissue diagnosis. Seven OSBC patients (22·5 per cent) had a frozen section biopsy, compared with three FTC patients (7·3 per cent).

Conclusion: The impact of OSBC has been variable and we believe the question "Is the one-stop clinic beneficial to the patient and is it cost effective", requires further appraisal and audit. Patient satisfaction will ultimately determine the continuation of this service, although the evidence that it has improved the clinical management of breast cancer remains to be proved.

Coloproctology 019

Comparisons of stapled and sutured anastomosis following ileocolonic resection for Crohn's disease

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Background: The aim of this study was to compare side-to-side stapled and standard end-to-end anastomosis following ileocolonic resection for Crohn's disease.
Method: One hundred and twelve patients requiring ileocolonic resection during the past 10 years have been reviewed.
Results: Forty patients had side-to-side stapled anastomosis (side-to-side staple line and both ends of bowels stapled transversely) and 72 underwent standard end-to-end sutured anastomosis. There were no complications related to anastomosis in the stapled group. The overall complication rate was 3 per cent in the stapled group compared with 25 per cent in the sutured group ($P=0{\cdot}005$). The overall recurrence rate at ileocolonic anastomosis was 1 of 40 (3 per cent) in the stapled group compared with 32 of 72 (44 per cent) in the sutured group ($P<0{\cdot}0001$). The overall reoperation rate for ileocolonic recurrence was 0 of 40 in the stapled group compared with 25 of 72 (35 per cent) in the sutured group ($P=0{\cdot}0003$). Using Kaplan–Meier methods, the cumulative recurrence and reoperation rates were lower in the stapled group compared with the sutured group ($P=0{\cdot}033$ and $P=0{\cdot}055$, respectively, log-rank test).
Conclusion: These data suggest that side-to-side stapled ileocolonic anastomosis for Crohn's disease is safer than sutured anastomosis and is associated with lower recurrence and reoperation rates.

Coloproctology 020

Management of severe third-degree obstetric tears: a multidisciplinary approach

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Background: Sphincter injuries following vaginal delivery are often repaired by inexperienced junior staff who have a poor understanding of the anatomy of the anal sphincters with up to 50 per cent of women describing some degree of subsequent incontinence and 85 per cent of women having a sphincter defect detected by anal ultrasound. The purpose of this study was to assess the short-term impact of involving a colorectal team in the management of patients with complicated severe third-degree tears.
Method: Over a 1-year period four women (age 29–31) with severe third-degree tears extending into the anal canal or rectum were referred to the colorectal unit for repair of the injury. Two were repaired immediately and two following formation of a defunctioning colostomy. The internal anal sphincter (IAS) was identified and imbricated. A nerve stimulator was used to help identify the external anal sphincter (EAS) which was repaired using an overlapping technique. The women were reassessed at 3 months with anal manometry and anal ultrasound. Further clinical assessment was performed at 1 year following colostomy closure.
Results: Two women were primigravidae. Episiotomy was performed in two and one had a forceps-assisted delivery. Birthweights ranged from 3·3–4·6 kg. Anal ultrasound revealed intact EAS repairs in all four women although IAS was thinned anteriorly in one. Resting anal pressures were slightly low (range 40–56 cmH_2O) but satisfactory squeeze pressures were obtained in all four women (range 95–100 cmH_2O). At 1 year, three were continent to solids, liquids and flatus, incontinence score = 0 (after Miller), but one had occasional urgency. The fourth experienced occasional liquid seepage and frequent incontinence to flatus likely to represent IAS dysfunction (incontinence score = 7).
Conclusion: Satisfactory short-term results may be achieved following repair of severe third degree tears and a nerve stimulator is important in identifying viable EAS to be used in repair. An integrated approach involving the experience of the colorectal team and anorectal physiology permits planning of future deliveries and may improve the long-term outcome.

Coloproctology 021

Colonic motility is abnormal before surgery for rectal prolapse

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Background: Fixation rectopexy (FR) remains the operation of choice for rectal prolapse (RP), recurrence rates are low but the functional results are poor. We measured hindgut motility before FR to determine whether an underlying neuropathy would explain this.
Methods: Seven females (age 56·5 ± 9·7 years) had a multilumen catheter inserted in the colon before FR. Colonic intraluminal pressure was recorded for a mean of 19 ± 3 hours; the number of peaks over 5 and 50 mmHg, motility and high amplitude propagated contractions (HAPC) measured before and after a meal and compared with five controls.
Results:

	Patients (SD)	Controls (SD)
Pre-prandial		
Contractions >5 mmHg	119 (55)	44 (32) $P=0{\cdot}03$
Contractions >50 mmHg	3·5 (3·4)	0·2 (0·4)
Motility	504 (359)	101 (65) $P=0{\cdot}03$
Post-prandial		
Contractions >5 mmHg	117 (53)	133 (131)
Contractions >50 mmHg	8·2 (15·9)	1·2 (1·1)
Motility	224 (151)	153 (122)

Patients have high numbers of >5 mmHg contractions and motility before meals. Controls respond to meals by increasing motility unlike patients. HAPC were seen in one patient but all controls.
Conclusion: These data show that patients with RP have a hindgut motility abnormality prior to FR, similar to that observed in spinal cord injury. This may explain the poor functional results after surgery offering a rational for colonic resection.

Coloproctology 022

Preliminary experience with coil embolization for major colonic haemorrhage

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Background: Although most patients with colonic bleeding settle with conservative measures, a proportion require emergency surgery which is associated with high morbidity and mortality. This study aimed to determine the safety and efficacy of coil embolization for the control of major colonic bleeding.
Method: Nine consecutive high-risk patients (three men, six women, mean age 81, range 72–87 years) with major colonic bleeding have undergone coil embolization. All had failed to respond to conservative measures (mean Hb at angiography 6·3 g despite mean transfusion volume of

6 units), were haemodynamically unstable at the time of angiography (mean systolic pressure 85 mmHg), and were destined for emergent laparotomy should embolization fail.
Results: In eight patients embolization achieved rapid haemostasis, with only one of these requiring further intervention for bleeding. Two of the eight subsequently developed ischaemic complications which were successfully managed conservatively. The ninth patient with Crohn's colitis required emergency surgery for continued haemorrhage, despite embolization of multiple left colonic bleeding points, and subsequently died
Conclusion: This experience demonstrates a role for coil embolization in the management of colonic bleeding where significant ischaemia is unlikely, provided the marginal artery is preserved. The use of these techniques in selected groups of patients can obviate the requirement for emergency surgery.

Coloproctology 023

Prolonged delayed healing pilonidal sinus wounds can be avoided

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Background: The aim of this study was to determine whether excision with primary closure of pilonidal sinus by a surgeon with a special interest could abolish delayed healing.
Method: We compared inpatient stay and time to healing in 102 pilonidal sinus patients treated by either wide skin excision and asymmetric primary closure (Karydakis procedure) carried out by one surgeon or laying open. Follow-up was from outpatient clinic records, and patient and GP questionnaires.
Results:

	Primary closure ($n=50$)	Lay open ($n=52$)	*P* value
Hospital stay (days) median (IQR)	7 (6–8)	2 (1–2)	Mann–Witney U-test <0·0001
Interval from operation to cessation of dressings (weeks) median (IQR)	3 (3–6)	6 (4–8)	Log rank <0·0003
No. patients unhealed at 10 weeks from operation	0	10	χ^2 0·003
No. recurrences	0	5	χ^2 0·073

Conclusion: Excision with primary closure resulted in a shorter period with dressings and fewer unhealed wounds, but involved a longer hospital stay compared with laying open. Prolonged delayed healing pilonidal sinus wounds can be avoided, however, as the Karydakis approach involved greater hospital cost and consultant input, patient selection becomes important and criteria for this need to be developed.

Coloproctology 024

Transanal resection for rectal carcinoma

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Background: A minimally invasive approach to rectal carcinomas may be appropriate for frail patients and those with advanced disease. Transanal resection (TAR) utilizes a modified urological resectoscope to resect rectal tumours.
Method: Since 1977, 143 patients (72 men, median age 78, range 38–92 years) have undergone 386 TARs (median two procedures per patient, range 1–17) and have been followed up for a median of 13 (range 0–240) months.
Results: The predominant indication for TAR was comorbidity (59), locally advanced disease (33), recurrent disease after previous anterior resection (16), metastatic disease (26) and villous tumours (9). The median distance of the tumours from the anal verge was 5 cm (range 1–15 cm). Twenty-eight major complications occurred (7 per cent of procedures, 20 per cent of patients): perforation (14), bleeding requiring reoperation (5), pneumonia (4), myocardial infarction (2) and incontinence (3), resulting in six early post-operative deaths. Sixteen patients (11 per cent) required a defunctioning stoma after TAR. Eleven patients (7 per cent) underwent subsequent rectal resection (six anterior resections and five abdomino-perineal excisions). The majority of patients (64 per cent) achieved satisfactory palliation of local symptoms. Median survival varied according to the indication for TAR: metastatic disease = 4 months, recurrent carcinoma = 13 months, locally advanced disease = 17 months, comorbidity = 19 months and villous tumours = 27 months. Ten patients were followed for over 3 years with no evidence of residual or recurrent rectal disease (median follow-up 50·5, range 36–240 months).
Conclusion: Transanal resection of rectal carcinoma is a useful technique in frail patients and those with advanced local or metastatic disease who would be expected to tolerate major surgery badly.

Coloproctology 025

Short course preoperative radiotherapy: experience using an Upsalla-type regime

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Background: A recent study using short course preoperative radiotherapy (DXT) has shown a significant reduction in local recurrence with an acceptable perioperative morbidity.
Method: We have audited our experience ($n=45$) along with the times from referral to DXT and then to surgery.
Results: The median time from referral to DXT was 36 (range 11–74) days and from DXT to surgery was 6 (3–42) days.

	Upsalla		North Trent	
	Preoperative DXT (%)	No DXT (%)	Preoperative DXT (%)	No DXT (%)
30-day mortality	2	2	6·6	5·1
Anastomotic leak rate	11	8	15·8 (3/19)	7·4
Perineal wound breakdown	20	10	24 (6/25)	<10?
No complications	56	66	55	?

Patients waiting longer than 7 days between DXT and surgery were more likely to suffer the major complications of anastomotic leak, wound sepsis or fistula formation, 6 of 13 (46 per cent) versus 6 of 32 (18·8 per cent).
Conclusion: These early results suggest that pre-operative DXT has a significant perioperative morbidity which is compounded by delays between radiotherapy and surgery. The long delays between referral and DXT highlight a major logistical problem in providing this service in North Trent.

Coloproctology 026

Glutaraldehyde proctitis: the cause of an outbreak of post-sigmoidoscopic diarrhoea

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Background: This study aimed to investigate the role of glutaraldehyde in an outbreak of post-sigmoidoscopic proctitis.

Method: An outbreak of bloody diarrhoea at the start of a flexible sigmoidoscopic screening programme prompted scrutiny of the incidence of this complication and the role of glutaraldehyde in its aetiology. The post-examination questionnaires completed 1 day after the sigmoidoscopy were reviewed for the first 400 subjects and glutaraldehyde levels in the recycled rinse water of the Auto-Disinfector 2 (Keymed) were measured. The incidence of symptoms in the subsequent 400 patients after installation of a new washer was examined.
Results: Five of the patients screened (1·3 per cent) presented to hospital with bloody diarrhoea occurring immediately after a normal examination. Sigmoidoscopy confirmed the presence of proctitis and stool cultures were negative. Symptoms rapidly subsided with steroid enemas. Eight additional patients (2 per cent) recorded similar problems but received no treatment and settled spontaneously. Glutaraldehyde levels rose progressively after each use of recycled 2 per cent glutaraldehyde solution (Cycle 1, 103 mg/l; Cycle 3, 445 mg/l; Cycle 5, 838 mg/l). No cases of proctitis were identified from the questionnaires completed by 400 patients after changing to a washer which did not recycle the rinse water.
Conclusion: Glutaraldehyde levels accumulate in recycled washing fluid and should be considered as a cause of post-sigmoidoscopic proctitis.

Coloproctology 027

Dynamic magnetic resonance defaecating proctography: a new method for assessing anorectal dysfunction?

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Background: The aim of this study was to develop a technique to investigate defaecatory dysfunction in the interventional magnetic resonance (IMR) scanner. This would combine functional evaluation with soft-tissue imaging in physiological positions without using ionizing radiation.
Method: Eight female patients (median age 63, range 21–83 years) were examined in a 0·5T IMR unit. Six patients had defaecatory difficulty including incomplete evacuation, excessive straining or the need for self-digitation. Examination was normal except for an anterior rectocele in two cases. One patient complained of faecal incontinence (examination revealed poor sphincter tone) and one had full thickness rectal prolapse. The patients were seated on a plastic bedpan with the anorectal region at isocentre and a loop transmit/receive coil under the bedpan. Gadolinium-DTPA (0·1 mmol/kg i.v.) was administered to aid bladder visualization in six patients. Dynamic real-time images were acquired at rest in mid-sagittal and coronal planes (FGR, acquisition time 4 s). Imaging was then performed during maximal squeeze and straining manoeuvres. This was followed by rectal administration of 200 ml of mashed potato reconstituted with 1 per cent gadolinium-DTPA in water. Whilst real-time imaging continued, the patients were asked to empty the rectum and signify when they felt defaecation was complete. The images were assembled into a cine loop for assessment of defaecatory dynamics.
Results: All patients tolerated the procedure. The pelvic organs and soft tissues were clearly visualized and rectal contrast was excellent. The levator ani muscles were visible in the coronal plane. No patient had asymmetrical levator contraction. Bladder visualization was improved by i.v. contrast. The rectal prolapse was clearly visualized. In five of the other patients an anterior non-emptying rectocele was identified, with intrarectal mucosal intussusception in two. Abnormal bladder neck descent was demonstrated in four patients. The patient with sphincter weakness was unable to retain the contrast material. In the final patient, failure of relaxation of the puborectalis (anismus) was demonstrated.
Conclusion: This technique evaluates defaecatory function in a physiological position without exposure to ionising radiation giving information concerning the function of the whole pelvic floor. The technique demonstrated a significant abnormality in patients with defaecatory dysfunction when physical examination was negative or inconclusive.

Coloproctology 028

To operate or not: 2-year outcome of colorectal cancer in a cohort of 1332 patients over 80 years old

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Background: This study aimed to determine the outcome at 2 years of a cohort of patients diagnosed with carcinoma of the colon and rectum between September 1991 and August 1994.
Method: A record of patients diagnosed with colorectal cancer within the Wessex region was interrogated and data analysed. The annual mortality for people over the age of 80 in the Wessex region was 24 per cent.
Results: One thousand and thirty-two patients were identified. Two hundred and ninety-nine patients did not have operative intervention: 82 were dead at the time of diagnosis (74 died as a result of cancer). Of the remaining 217 (mean age 87 years, 69 men), 39 refused operation, 83 were deemed too ill, 39 were inoperable and in the rest no reason was given for non-operative treatment. At 2 years, 159 patients had died (73 per cent). The median time of death was 41 days after diagnosis (range 1–730) and in 124 (78 per cent) the cause of death was attributable to their cancer. Of those who refused operation, 30 per cent were alive at 2 years. In those deemed too ill for intervention, 24 per cent were alive which was similar to the 30 per cent survival in those deemed inoperable. One thousand and thirty-three patients (mean age 85, 43 per cent men) had surgery for their cancer. At operation, 7 per cent had disseminated disease and no resection was done, 6 per cent had local excision, 28 per cent had right, 6 per cent extended right, 2 per cent transverse, 6 per cent left and 11 per cent sigmoid colectomies, while 10 per cent had anterior resection of the rectum, 6 per cent abdominoperineal resection, 2 per cent subtotal colectomy, 7 per cent had a Hartmann's procedure. In 9 per cent the procedure done was not known. Eleven per cent had Dukes classification A, 41 per cent Dukes B, 20 per cent Dukes C staged disease and 22 per cent had liver deposits. Ten per cent of patients developed chest infections. There was an anastomotic leak rate of 2 per cent, 2 per cent postoperative haemorrhage, 2 per cent pulmonary emboli, 3 per cent myocardial infarction, 2 per cent bowel obstructions, 5 per cent wound infections, 1 per cent developed a deep vein thrombosis. The 30-day mortality was 16 per cent. At 2 years 50 per cent of patients had died [median time of death: 157 days after operation (range 0–725)].
Conclusion: These results show that operative intervention for colorectal cancer improves survival in patients over the age of 80.

Coloproctology 029

Aspirin, sulindac and the rectum in familial adenomatous polyposis

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Background: This study was designed to investigate the effect of aspirin and sulindac, both non-steroidal anti-inflammatory drugs (NSAIDs), on the rectum of patients with familial adenomatous polyposis (FAP).
Method: Six patients with FAP who had previously undergone colectomy with ileo-rectal anastomosis were randomized to receive 3 months' treatment with aspirin and then sulindac or sulindac and then aspirin. There was a 1-month wash-out between treatments. Videotape recordings of the rectum were taken to permit polyp counts pre- and post-intervention and mucosal biopsies for assessment of crypt cell proliferation by mitosis counting following whole crypt microdissection.
Results: Treatment with both NSAIDs resulted in reductions in crypt cell proliferation in flat rectal mucosa but the effect was more marked with sulindac (decreased from a mean of 11·7 to 6·8 mitotic cells/crypt, $P=0{\cdot}038$) than with aspirin (decreased from a mean of 13·2 to 10·3, $P=0{\cdot}027$). Mean polyp counts also decreased after both sulindac and aspirin treatment, from 15·7 to 10·2 and 13·1 to 12·1, respectively, but this did not reach statistical significance.

Conclusion: Both aspirin and sulindac reduce proliferative activity in the macroscopically normal mucosa as assessed by whole crypt microdissection. This does not result in a concomitant regression of adenomatous polyps over the time scale studied.

Coloproctology 030

Training in coloproctology. How much actually takes place?

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Background: To assess trainee experience and consultant supervision in coloproctology in a UK city.
Method: Coloproctology operations undertaken during 1996 were retrieved from a prospective regional database containing all general surgical operations. The database covered three teaching hospitals, 15 consultants, 11 specialist registrars (SpR) and 11 SHOs.
Results: A total of 2464 coloproctology operations (excluding appendix operations) were undertaken. Eight hundred and seventy-two (35 per cent) were performed by a consultant who assisted in another 15 per cent. One thousand and seven (41 per cent) were undertaken by a registrar and the consultant assisted in one third. Two hundred and fifty-five (10 per cent) were undertaken by an SHO and the consultant assisted in 20 per cent. Individual consultant supervision ranged from 7 to 29 per cent. In a larger audit consultants assisted in 19 per cent of colorectal cancer resections and their supervision appeared to be increasing. Analysis of representative operations on the general surgical units suggested that an SpR would, on average, undertake 1·4 Hartmann's resections per year (50 per cent consultant supervised) and an SHO 3·1 haemorrhoidectomies per year (33 per cent consultant supervized).
Conclusion: This study suggested that trainees received minimal coloproctology training from their consultants. There is considerable scope for consultants to increase their supervision but this will have significant service implications.

Coloproctology 031

Towards early appropriate referral for the diagnosis of colorectal bleeding

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Background: The aim of this study was to audit the quality of general practitioner's (GP) referral letters with regards to rectal bleeding and to implement necessary changes to improve the data presented.
Method: Rectal bleeding referral letters between January 1996 and December 1996 from all GPs in a specific area were reviewed and scored using a simple scoring system. An educational programme in respect to colorectal disease and rectal bleeding was implemented to involve all GPs and practice nurses.
Results: Sixty-four (37 from men) referral letters have been analysed. Details of colorectal symptoms with duration and clinical examination findings in the referral letters were allocated appropriate points (maximum score being 17 points). The mean score of the letters was only 3·2 (range 0–15) points. Only 12 GPs had documented evidence of abdominal examination and 24 had documented rectal examination findings. Hospital investigations confirmed four cancers, 11 polyps, five colitis, one solitary rectal ulcer, 10 diverticular disease, 26 haemorrhoids, six fissures and two fistula-in-ano. Three patients were inappropriately referred and had no colorectal symptoms (back pain, heartburn, ovarian mass). PSB and CB have visited all 18 practices and spoken individually to 36 GPs (out of 45) and 31 nurses. A total of 136 miles have been covered and 42 h have been spent directly on educational meetings. After completion of GP visits a symposium was organized to answer any remaining questions and to develop further the theme of colorectal cancer. Eighteen GPs attended the symposium and over 90 per cent found it very useful and educational.
Conclusion: The educational programme has been well received by both GPs and nurses. Re-evaluation of referral patterns will indicate the success of the educational programme and, in fact, recent referral letters have been of high quality.

Coloproctology 032

Controlled intraoperative water testing of left-sided colorectal anastomoses: are ileostomies avoidable?

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Background: Anastomotic leakage is a major problem in colorectal surgery, and previous studies have suggested that intraoperative identification of leaks allows repair at the time of surgery. This study examined whether testing allowed a defunctioning ileostomy to be safely omitted.
Method: One hundred and two consecutive patients underwent left-sided colorectal resection (52 males and 50 females with a mean age o 65·7, range 16–89, years). Following completion of anastomosis, it integrity was tested by running saline into the rectum, using a manometer to a maximum distending pressure of 30 cm water. Any leaks were repaired and the anastomosis re-tested. All patients underwent a contras enema on the eighth postoperative day. A defunctioning ileostomy wa only performed if the anastomosis could not be shown to be leak-proo on testing.
Results: Twenty-one (20·6 per cent) patients failed the initial leak tes although only two of these went on to have a clinical leak. Sixteen (16· per cent) had a leak on radiological testing, and there was clinical evidence of a leak in five (4·9 per cent) patients. Two defunctionin ileostomies were performed. There were three (2·9 per cent) deaths bu none of these had a leak on radiological testing.
Conclusion: Incomplete anastomoses were successfully corrected intraoperatively. A defunctioning ileostomy was avoided in 98 per cent o cases.

Coloproctology 033

Systematic review of laparoscopic surgery for malignant colorectal disease

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Background: A systematic review of the current literature on laparoscopic surgery for colorectal malignancy was undertaken to compare th complications, postoperative outcome, survival and cost of laparoscopi surgery for colorectal malignancy with open surgery.
Method: Publications from January 1991 to March 1997 were located b electronic database, manual and reference search. Inclusion criteria wer used to select the most robust studies which were weighted by hierarchy o evidence for the review. Data were abstracted to a database for analysis.
Results: Of the 157 publications located, only 42, representing 341 patients, were selected for inclusion into the review. All were low in th hierarchy of evidence (32 were case series reports). Only 13 of the 4 papers concentrated specifically on malignant disease. The average patien age was 63·2, equal male to female ratio. The most common contraindications were bulky tumour masses, previous operations or obesity. Th operative conversion rate for a range of procedures was 17·2 per cen Intraoperative complication rate was 4·2 per cent, postoperative morbidit was 11·3 per cent and 30-day mortality was 1·64 per cent. No circumferential margins were reported; the average distal margin was 5·7 cm an average lymph node harvest was 10·4. Recurrence rates, reported by ha the papers, was 8·4 per cent, one tenth were port-site metastases. We wer unable to assess critically recovery benefits, long-term survival or cost.
Conclusion: Studies of low hierarchy of evidence continue to be published 6 years after the first report of laparoscopic colorectal surgery wit the majority of papers representing feasibility studies which cannot b generalized and are highly variable in the standard of reporting, reflectin a non-standardized approach to the reporting of a new technique. Th benefits of laparoscopic surgery for malignancy remain unproved an should only be undertaken in the context of a multi-centre randomize controlled trial.

General 017

A prospective comparative audit of emergency surgical workload at a district general hospital over changing times

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Background: This study aimed to assess the impact of recent national changes on surgical training at a district general hospital.
Method: Five hundred and fifty consecutive emergency surgical referrals for the 9-week period 1 September to 3 November 1995 and 543 consecutive emergency surgical referrals for the same 9-week period in 1996 were studied. Statistical analysis was performed using the χ^2 test.
Results: At senior house officer level exposure to acute surgical referrals was reduced by 52 per cent and at career specialist registrar level by 4 per cent. In 1996, 3 per cent fewer patients were operated upon and there was a 10 per cent fall in attendance of the admitting trainee at these operations.
Conclusion: The results indicate a significant ($P<0{\cdot}001$) deleterious impact of the changes between 1995 and 1996 on training opportunities in the surgical department of a district general hospital at senior house officer level.

General 018

A prospective audit of inguinal hernia in childhood

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Background: The aim was to assess the management of inguinal hernia repair in children.
Method: All children admitted for repair of an inguinal hernia were audited prospectively, assisted by the clinical audit department.
Results: In a 4-month period, 135 children were identified. Of these, 72 (53 per cent) were under 1 year of age, of whom 39 (54 per cent) had been born prematurely. In 45 (33 per cent) cases, the child required emergency admission for suspected incarceration of the hernia. In those under 1 year, however, 38 (53 per cent) were emergencies. A consultant surgeon performed or was present at 73 (54 per cent) cases and in 45 (63 per cent) of those children under 1 year; a consultant anaesthetist was present at 109 (81 per cent) cases and 63 (88 per cent) of those under 1 year. Complications related to surgery were identified in six (4 per cent) children, none of which required a further procedure. The mean length of hospital stay in all children was 1·6 days (range 1–4 days) for elective admissions and 2·4 days (1–7) for emergency cases. In those under 1 year of age, this was 1·8 (1–4) and 3·5 (1–7) days, respectively. This longer stay in emergency cases was due mainly to the difficulty in finding an appropriate theatre session. Prematurity was the commonest cause for an overnight stay.
Conclusion: When planning hernia surgery in children, half could be expected to stay for at least one night. Inguinal hernias in infants continue to require emergency treatment and urgent referral of children in this age group to a paediatric surgeon is once again recommended.

General 019

Diagnostic laparoscopy for appendicitis: only useful in young women

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Background: A prospective audit of diagnostic laparoscopy for patients with suspected appendicitis was revisited after 2 years to 'close the loop' for effective clinical guidelines. Open appendicectomy is encouraged as a training operation at this Trust.
Method: Between January 1995 and December 1996, 282 patients were taken to theatre with a diagnosis of suspected acute appendicitis. Of these 145 (51 per cent) had laparoscopy; 116 had subsequent appendicectomy. The remaining 137 patients (49 per cent) had appendicectomy without preliminary laparoscopy (the majority being men or children with clear signs and symptoms).
Results: Twenty-nine patients were spared unnecessary appendicectomy following laparoscopy, all but one being women of child-bearing age. However, 116 patients had appendicectomy of whom 31 (21 per cent) had a clinically and histologically normal appendix; 85 (59 per cent) were inflamed with 23 (16 per cent) perforations. Of those who did not have laparoscopy 29 (21 per cent) had a normal appendix removed, 108 (79 per cent) were inflamed with 35 (32 per cent) perforations. Operating times were prolonged in the laparoscopy group (62 min; range 2–240 min) compared to open operation alone (53 min; range 15–250). There were no differences in length of post-operative stay (4·2 days, range 1–16 versus 4·6 days, range 1–17).
Conclusion: Although the negative appendicectomy rate was similar it is clear that women of child-bearing age benefit from preliminary diagnostic laparoscopy to avoid unnecessary operation. For all other patients open appendicectomy is appropriate and should be retained as a training operation.

General 020

Delivery of surgical care in a district general hospital without High Dependency Unit facilities

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Background: Many hospitals lack the facilities for high dependency care, and patients requiring this level of care are nursed on the surgical ward. The aim of this study was to assess the extent of this problem in a district general hospital, looking at the impact of providing High Dependency Unit (HDU) care at ward level.
Method: A 28-bed surgical ward was studied for 39 consecutive days. Patients were assessed as being either appropriately placed (routine) or inappropriately placed (HDU). Nursing interventions and observations over each 24-h period were recorded for the most dependent patient in each group.
Results: Data were collected for a total of 1092 bed days. Median bed occupancy was 22 patients (78 per cent). Inappropriately placed HDU patients accounted for 55 bed days (5·04 per cent, average 1·4 patients/day). These patients required more intensive nursing than routine patients. HDU patients received more observations during 24-h than routine patients (mean 11·33 and 4·15, respectively, $P<0{\cdot}005$). The number of observations recorded for a routine patient in 24-h fell when an HDU patient was nursed concurrently on the ward (average 5·09/24 h, falling to 3·77/24 h in the presence of an HDU patient, $P<0{\cdot}02$).
Conclusion: HDU patients require more intensive nursing care than routine surgical patients. The nursing of HDU patients on the ward adversely affects the quantity of care available for less dependent patients.

General 021

A profile for change: improved operating theatre utilization

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Background: In keeping with the findings of the Bevan report of 1989 towards greater operating theatre efficiency, we set out to design and test a software system aimed at profiling the annual performance of each individual inpatient operating session for nine general surgeons in a large district general hospital.

Method: A software system was designed to employ standard information collected in an existing theatre database (ORSOS) and to display the results for each operating session for a year in simple graphic and tabular form on a single sheet of paper. Data were produced concerning theatre time utilization ('set-up time', 'operating time', 'de-set-up time', 'cold table time', early and late starts and finishes), number of patients and case-mix by BUPA category, intermediate equivalent procedures per session, total lists used and cancelled cases per annum. These data completed a profile of the working patterns of each individual operating list and hence theatre team (surgeon, anaesthetist, nursing and ancillary staff), enabling identification of persistent problems of case-mix, case-load, cancellations and surgical, anaesthetic, nursing or portering delays. Individual profiles were distributed to surgeons, anaesthetists, theatre sisters and theatre managers involved with each session, for interpretation, discussion and subsequent implementation and assessment of any changes towards improved practice.
Results: After running the profiles for two years, there has been an overall increase of 3·5 per cent in the mean intermediate equivalent value of each session, a 12 per cent reduction in lists finishing more than 30 min early and an increase in the total number of cases of 9 per cent, with a 10·7 per cent reduction in cancelled cases. The percentage utilization of theatre sessions for individual surgeons increased in a significant majority to over 90 per cent, representing a 5·3 per cent increase in overall theatre utilization (91·3 per cent), a calculated saving of £100,000 in reduction of wasted theatre time.
Conclusion: From the outset it was determined that the project would be strictly facilitatory rather than judgmental and through individual and group discussion of these profiles, problems have been addressed and changes implemented to improve overall operating theatre efficiency.

General 022

Longevity of surgeons

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Background: The aim of this study was to reveal the mean retirement and survival (MS) of surgeons in relation to other doctors.
Method: A study of 1488 obituaries reported in consecutive British Medical Journal issues was made from February 1992 to November 1995.
Results: General practitioners led the list of reported deaths (558 doctors) with MS of 74·49 years, followed by physicians (326) 77·94 years, then surgeons (226) 76·05 years. Others included ophthalmologists 77·58, and accident/emergency surgeons 64·5, psychiatrists (70) 71·6, anaesthetists (65) 73·34, pathologists (62) 77·19, obstetricians/gynaecologists (60) 74·89. There were eight medical students and trainees with the shortest MS of 24 years. The 10 reported hospital administrators have the longest MS of 78·68 years. Of 226 surgeons, 41 died while working (18·5 per cent) with MS of 55 years, 17 retired before the age of 65 (7·5 per cent) with a late MS of 11·82 years, 161 retired at the age of 65 (71 per cent) with a late MS of 15·06 years, and seven continued their private practice after the age of 65 (3 per cent) with a late MS of 10·85 years.
Conclusion: Surgeons survive well as compared to other doctors, but physicians and administrators are the longest survivors. There is no clear evidence that surgeons who retire early survive longer. Retirement at 65 can still yield an optimal survival.

General 023

When is the specialist surgeon really trained?

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Background: Surgical training and experience are frequently claimed to influence surgical results. The aim of this study was to quantify any improvement in an individual surgeon's performance in one operation over a period of 8 years from initial appointment to date.
Method: Patients undergoing Ivor–Lewis subtotal oesophagectomy performed by a single surgeon (SMG) between November 1989 and January 1997 were identified from a prospectively compiled oesophageal cancer database. Age, sex, smoking and alcohol history, ASA grade, operative time (abdominal, thoracic and 'one lung time'), blood loss, transfusion requirements (intraoperative and total), extent of lymphadenectomy (number of lymph nodes sampled, ITU stay, postoperative complications, pathological stage, grade and survival were studied. Statistical comparison was carried out using ANOVA and χ^2-squared tests.
Results: The records of 150 patients were identified for analysis; the cohort was split into five groups of consecutive patients. Each of the groups was comparable for age, sex, smoking and alcohol histories, ASA grade, and histological stage of disease. Analysis of the variables pertaining to operation revealed a significant improvement with time:

Cases	One lung time (min)	Blood loss (ml)	Transfusion (units)	ITU stay (days)	In-patient stay (days)	Lymph nodes sampled (*n*)
1–30	120·2 (6·3)	1186·7	2·07 (0·37)	4·89 (0·88)	27·8 (2·3)	8·03 (0·78)
31–60	121·6 (3·8)	1332	1·64 (0·51)	3·93 (1·4)	22 (2·7)	11·61 (1·6)
61–90	110·1 (3·9)	815·3	0·31 (0·15)	2·73 (0·57)	29 (5·17)	12·29 (1·05)
91–120	104·1 (5·6)	790·7	0·29 (0·14)	2·75 (1·06)	22·1 (5·36)	15·96 (1·36)
121–150	99·7 (7·5)	879·2	0·76 (0·21)	1·08 (0·13)	16·1 (0·70)	15·29 (1·5)
P value	0·03	<0·01	<0·001	0·02	0·04	0·002

Conclusion: This study reveals a continuing improvement in an experienced surgeon's operative performance over 8 years. With the current trend to a shorter training for surgeons, there is a case for continuing supervision of the 'fully trained' surgeon undertaking complex procedures.

General 024

Audit of the 841 deaths from oesophageal or gastric cancer on surgical wards in Scotland 1994–1996

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Background: The Scottish Audit of Surgical Mortality (SASM) collected data on all 841 patients (395 with oesophageal cancer, 446 with gastric cancer) who died on surgical wards from 1994 to 1996.
Method: Five hundred and six (60 per cent) were <70 years (range 30–96 years), 61 per cent were men and 55 per cent were admitted as an emergency. Emergency admission increased with age. Seventy per cent of patients were ASA 3 or greater. The cause of death was cancer in 53 per cent but cardiopulmonary complications in 21 per cent; 451 died without an operation. A post-mortem was done in only 18 per cent and provided additional information in 33 per cent of patients.
Results: Case note review showed close agreement between the surgical and anaesthetic assessors. From surgical assessment, the choice of operation (3·9 per cent) preoperative management (2·8 per cent), intraoperative management (11·1 per cent), or postoperative management (8·8 per cent) contributed to death. There were technical problems in 20 per cent of the operations. Anaesthetic criticisms included the failure to use ITU/HDU (in 22·5 per cent) and postoperative management in 8·5 per cent. Adverse surgical decisions contributed to death in 16·2 per cent (1994) falling to 12·8 per cent (1996), and caused death in 5·1 per cent (1994) falling to 0·7 per cent (1996); anaesthetic factors contributed to death in 10·1 per cent and caused death in 1·0 per cent.
Conclusion: This SASM Audit highlighted problem areas in the surgical management of patients with oesophageal and gastric cancer and resulted in improved surgical decision-making. There remains room for improvement particularly for intraoperative and postoperative care in patients with operable disease.

General 025

Surgical patients with multiple-resistant *Staphylococcus aureas* infection: a P-POSSUM analysis

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Background: This study aimed to study the significance of multiple-resistant *Staphylococcus aureas* (MRSA) infection in surgical patients using the P-POSSUM scoring system.
Method: All surgical patients were prospectively scored using the P-POSSUM. A subset of these patients with MRSA infection were analysed using P-POSSUM predicted mortality, comparing physiological and operative severity score with non-MRSA surgical patients and length of hospital stay with P-POSSUM-matched non-MRSA controls.
Results: Thirty of the 1132 patients were MRSA positive and of these five died giving a P-POSSUM observed/expected deaths ratio of 1·7 (not significant; 95 per cent, CI –0·24–0·10). The P-POSSUM physiology score of 30 MRSA-positive patients compared to the non-MRSA group (n = 1102) was significantly worse (20·9 versus 17·4; 95 per cent, CI 1·09–5·95) as was the operative severity score (15·6 versus 9·2; 95 per cent, CI 4·40–8·42). The length of stay for MRSA-positive patients was significantly longer than P-POSSUM-matched controls. For mortality risk <5 per cent (n = 16), mean hospital stay (days) MRSA-positive controls = 23·8 versus 5·9; 95 per cent, CI 2·42–33·48. For mortality risk >5 per cent (n=9), mean hospital stay (days) MRSA-positive controls = 33·4 versus 13·4; 95 per cent, CI 5·50–34·64.
Conclusion: MRSA infection in surgical patients does not increase mortality. However, patients who have contracted MRSA infection are more debilitated, undergo a greater surgical insult and stay longer in hospital compared to the non-infected controls.

General 026

A dedicated NHS hernia service improves patient outcome and cost-effectiveness

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Background: A hernia service was commenced at Derriford Hospital on 1 October 1996 following a poor star rating for its performance in day-case hernia surgery. The rationale was to increase the number of patients undergoing day-case, local anaesthetic surgery and to improve cost-effectiveness.
Method: The number of patients undergoing day-case and local anaesthetic repair since the commencement of the hernia service to July 1997, was identified. A hernia satisfaction questionnaire was sent to a random sample of 50 patients who had had their hernia repaired by the hernia service and 50 patients who had had their hernia repaired by another team.
Results: In its first 9 months, 207 men were referred to the service and 156 (145 primary and 11 recurrent) had undergone hernia repair, 117 (75 per cent) went home the same day. Local anaesthesia (LA) was used in 128 (82 per cent), 110 (86 per cent) of whom went home the same day compared to seven (30 per cent) who received a general anaesthetic (GA). Completed questionnaires were received from 41 (82 per cent) hernia service patients and 36 (72 per cent) patients treated by another team. Results were analysed for 36 patients from each group. Of the second group, 13 (36 per cent) received LA and 14 (39 per cent) were treated as a day-case. Hernia service patients experienced a mean pain score of 4·7 (range 0–10) compared to 5·7 (range 0–10) (P = 0·07) for the other group. Hernia service patients required postoperative analgesia for a mean of 2·8 days (range 0–6 days) compared to 5·9 (0–21 days) (P<0·01) in the other group. Similarly, hernia service patients experienced wound pain for a mean of 3·4 days (0–21) compared to 8·1 (0–30) (P<0·01) for the other group. Normal activity was also resumed at an earlier stage by patients treated by the hernia service (mean 10·8 days compared to 17·6 days, P<0·01).
Conclusion: These results demonstrate that the instigation of a hernia service has resulted in more patients undergoing local anaesthetic, day-case surgery with less postoperative pain and an earlier return to normal activity. Increasing the number of day-case hernia repairs from 39 per cent to 75 per cent in this hospital (800 adult hernia repairs annually) represents an annual saving of over £70 000.

General 027

Analgesia in acute abdominal pain: an audit of current surgical practice

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Background: Traditional teaching states that analgesia should be withheld in patients with acute abdominal pain for fear of masking physical signs. Others argue that such practice amounts to suboptimal clinical management. As approximately 25 per cent of all surgical admissions require treatment of acute abdominal pain, this study aimed to: i) determine local surgical practice for pain relief; and ii) investigate patient, clinician and hospital dependent factors which might influence variability in patient waiting times for analgesia.
Method: One hundred emergency admissions with acute abdominal pain were randomly selected for analysis. Time of analgesia administration, clinical setting of first dose, and clinical diagnosis were documented. Pain severity was determined by visual analogue patient self-assessment. Local surgical opinion as to the appropriate timing of analgesia was acquired by questionnaire, and determined for all grades of surgical staff (n = 35 of 36).
Results: Forty per cent of patients received analgesia within 1 h of admission, 17 per cent between 1–2 h, but 43 per cent waited 2–20 h for first dose of analgesia. Analgesia was not withheld in any patient to facilitate diagnosis. Eighty-four per cent of patients (n = 84) had severe pain and 16 per cent moderate pain. Mean waiting time for analgesia in severe pain was 2·3 h versus 6·3 h for moderate pain (P<0·0001; Wilcoxon). However, 33 per cent with severe pain waited >2 h for analgesia. Clinical diagnosis did not influence the urgency with which analgesia was administered, regardless of the pathology. Local surgical opinion favoured early analgesia after the initial SHO assessment ('yes' 88 per cent; n = 30), even in the absence of a firm diagnosis ('yes' 79 per cent; n = 37). The majority of surgical staff believe that early analgesia does not mask physical signs ('no' 62 per cent; n = 21). However, junior surgical staff (SHOs) were most likely to withhold analgesia in the accident and emergency department (A&E) for fear of masking physical signs. Patients leaving A&E without analgesia waited on average 5·7 h for first dose of analgesia compared with 0·9 h for those receiving analgesia in A&E (P<0·0001; Wilcoxon). Ninety-two per cent of GP referrals did not receive pre-hospital analgesia.
Conclusion: Forty-three per cent of admissions with acute abdominal pain wait too long, despite local surgical opinion advocating early analgesia. Severity of pain and underlying pathology do not influence early pain relief. The huge variability in patient waiting-time for analgesia results from omission of analgesia in A&E, and a fear of hampering clinical management by junior surgical staff at SHO level.

General 028

Surgical assessment wards: the way forward?

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Background: The aim of this study was to use the general surgical bed complement more efficiently and to improve emergency services. Emergency surgical admissions are concentrated on one ward, the Surgical Assessment Ward (SAW). We describe the results and impact of the SAW since its introduction in 1996.
Method: Data were collected and analysed for all surgical emergencies for the year before SAW was opened (1994–1995) and the year since its introduction (1996–1997).

Results: The total length of stay for emergency admissions has decreased from 14 281 to 13 809 despite a 2·6 per cent increase in the number of admissions. There was a 21 per cent increase in the number of patients allowed home within 24 h of assessment in 1996–97. Nevertheless, there was an increase in the number of emergency procedures performed from 1342 to 1442. The mean number of consultant visits to the SAW per day was three. There was an increase (10·4 per cent) in the total number of elective surgical admissions from 4596 to 5076 and an increase in the percentage mean bed occupancy in general surgical wards from 73 per cent to 80 per cent.

Conclusion: The SAW concentrates emergency services on one ward, thereby facilitating admissions by GPs and increasing the efficiency of elective surgical work. The implementation of the SAW may have saved £84 300 in the year 1996–1997.

General 029

Validation of the P-POSSUM surgical scoring system in a district hospital

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Background: P-POSSUM (Portsmouth-POSSUM) was described in 1996 as an improvement on the POSSUM surgical scoring system (POSSUM = Physiological and Operative Severity Scoring System in the enUmeration of Morbidity and mortality). The aim of this study was to assess the performance of P-POSSUM in a district hospital to check the validity of its predictions in an independent unit.

Method: Between November 1996 and April 1997, 1132 general surgical patients who underwent an operation were prospective scored by the P-POSSUM system. End-points were death or discharge. One audit clerk, specifically employed for this project, collected the P-POSSUM data daily and added it to a dedicated computer database.

Results:

Risk range	Number at risk	Mean risk	Predicted deaths	Reported deaths	χ^2
0–<5	1025	0·9	9	7	0·45
5–<15	65	8·74	6	7	0·18
15–<50	34	25·88	9	7	0·60
50–100	8	67·25	5	3	2·13
0–100	1132	2·27	29	24	$P = 0{\cdot}50$ (4 d.f)

Conclusion: There was an excellent correlation between the number of reported and P-POSSUM predicted deaths. This study validates the mortality prediction by P-POSSUM in a second district hospital.

General 030

Current surgical practice in the management of inguinal hernias in the UK

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Background: This study aimed to establish current surgical practice in the management of inguinal hernia in NHS patients and to compare this with the guidelines published by the Royal College of Surgeons of England.

Method: All surgeons and hospitals in two regions (South Thames and Northern & Yorkshire) performing groin hernia repair were identified and invited to participate. Participating surgeons completed a questionnaire for all patients over 18 years undergoing elective and emergency inguinal hernia between July and October 1996.

Results: Three hundred and eighty-five surgeons in 131 hospitals were identified. Of these, 118 hospitals were included and 276 of 368 (75 per cent) surgeons in these hospitals agreed to participate. Questionnaires in 5038 of 5556 patients were returned (90·7 per cent) of whom 4212 had inguinal hernia repairs in the NHS. One hundred and seventeen (2·8 per cent) operations were performed on urgent or emergency cases. A consultant operated on 1554 (37·4 per cent) patients and 259 (6·1 per cent) of operations were performed by unsupervised SHOs. A total of 2416 (61·1 per cent) patients received antibiotics. Two hundred and twenty-seven (5·4 per cent) operations were performed using local anaesthesia and 1745 (42·5 per cent) were as planned daycases. Consultant surgeons did not perform significantly more day-case operations. The operative techniques are shown in the Table. Consultant surgeons performed 282 (18·2 per cent) of operations laparoscopically ($P < 0{\cdot}001$ χ^2).

Operative technique	Number (%)
Shouldice	430 (10·2)
Lichtenstein	2944 (69·9)
Stoppa	64 (1·5)
Bassini	390 (9·3)
Nylon (or similar) darn	367 (8·7)
Prosthetic plug	53 (1·3)
Total laparoscopic	407 (9·7)
TAPP laparoscopic	315 (7·5)
TEP laparoscopic	82 (1·9)
Other laparoscopic	10 (0·2)

Conclusion: There has been a large change in practice in recent years that coincides with publication of the RCS guidelines. There was very widespread uptake of open mesh repair. The use of local anaesthesia is very low. Many patients had prophylactic antibiotics despite there being little evidence of benefit. Laparoscopic surgery was carried out by senior surgeons which may improve outcomes but might have implications for training.

General 031

Is your anaesthetist nauseating?

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Background: Postoperative nausea and vomiting (PONV) can increase hospital stay and decrease patient satisfaction. The aim of this study was to reduce the incidence of PONV after varicose vein (VV) surgery.

Method: Some 57 patients (39 women, median age 54 years) had VV surgery performed by a single consultant vascular surgeon. Twenty-one patients had a unilateral procedure, 33 bilateral and three had surgery for recurrent VV. All patients were anaesthetized by one of three consultant anaesthetists (A, B and C) who used different techniques. No attempt was made by the surgeon to influence the anaesthetic. After surgery, each patient gave categorical answers about PONV. The anaesthetists were given the results and told that it would be repeated without their knowledge. One month later, 42 patients (median age 48 years, 34 female, 16 unilateral, 24 bilateral, two recurrent) were entered into an identical study. Results were analysed by χ^2.

Results: In the first study, anaesthetist A treated 15 patients of whom six (40 per cent) felt nauseated and one (7 per cent) vomited, B treated 26 patients, 15 were nauseated (57 per cent) and five (19 per cent) vomited and C treated 16 patients, one was nauseated (6 per cent), none vomited. C produced significantly less nausea compared with both B ($P = 0{\cdot}03$) and A ($P = 0{\cdot}0009$). No significant differences were observed between A and B and there were no differences in vomiting. In the second study all three anaesthetists used the technique employed by C. A treated 11 patients, one (9 per cent) had nausea, none vomited, B treated 17 patients, one (6 per cent) had nausea, none vomited, C treated 14 patients, one (8 per cent) had nausea, none vomited. There was an improvement from the previous study for both A ($P = 0{\cdot}08$) and B ($P = 0{\cdot}0006$).

Conclusion: This study shows that surgeons can influence the outcome of anaesthesia to the benefit of their patients.

Vascular 041

Outcome in patients requiring renal support following repair of ruptured aortic aneurysm

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Background: The aim of this study was to assess the outcome of patients requiring renal support following repair of ruptured aortic aneurysm.
Method: Retrospective audit of all patients developing acute renal failure following emergency aortic aneurysm repair between 1984 and 1996.
Results: Sixty-five patients developed acute renal failure following emergency aortic aneurysm repair over 13 years, with a median age at presentation of 68 (range 49–84 years). The overall 30-day mortality in this group of patients was 75 per cent. Three prognostic indicators were identified as being associated with a significantly higher mortality rate in these patients: the presence of vascular disease at presentation (other than the aneurysm), the need for an additional intraoperative procedure and the presence of one or more failing organ systems. The mortality increased to 95 per cent when all three factors were present. Renal replacement therapy was required for a median of 11 (range 0–41 days) in non-survivors and median period of 19 (range 1–46 days) in survivors. Sixteen survivors were discharged from hospital after a median stay of 49 (range 10–137 days). Postoperative serum creatinine was >130 µm/l in 11 of these patients. A further patient was dialysis dependent. Survival following discharge was 100 per cent at 6 months.
Conclusion: Acute renal failure complicating ruptured abdominal aortic aneurysm is associated with a 75 per cent in-hospital mortality. The mortality rate increases to 95 per cent if there is a history of vascular disease, an additional operative procedure is performed and one or more organs fail postoperatively.

Vascular 042

Ruptured abdominal aortic aneurysm in the octogenarian

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Background: The role of emergency aortic surgery for ruptured aneurysm in the over 80 years age group is controversial with some advocating an 'all-comers' policy, some a selective policy and others suggesting that surgery is usually not justified. We wished to examine the outcome of an 'all-comers' policy to ruptured aneurysms in the octogenarian.
Method: All confirmed ruptures in patients over 80 at the time of presentation (mean age 83·3 ± 2·4; range 80–88 years) to one vascular surgeon were included in this study over a 5-year period. Twenty-six patients were identified, of whom three patients did not have surgery, one due to pre-theatre death and two patients who had known terminal illness.
Results: In 23 elderly patients having surgery there were 15 survivors at 30 days (65 per cent). Perioperative deaths were due to myocardial infarct (3), multi-system failure (3) and respiratory failure (2). There was no significant difference in mortality rate between patients in this study and a contemporaneous series of 117 ruptures of all ages. Mean follow-up was 3·3 years with four further deaths occurring at 3 months, 5 months and 60 months after discharge.
Conclusion: These data suggest that emergency repair of ruptured AAA in the elderly patient carries a similar initial chance of survival compared to a younger patient and is entirely justified.

Vascular 043

Ruptured abdominal aortic aneurysms: perioperative factors influencing outcome

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Background: Comparative audit reveals a considerable variation in mortality from emergency repair of ruptured abdominal aortic aneurysm that is often attributable to case mix. This study aimed to identify the most important factors that are predictive of early mortality following emergency repair of ruptured abdominal aortic aneurysm.
Method: The hospital records and operative notes of 102 consecutive patients, who underwent emergency surgery for ruptured AAA, were reviewed retrospectively. Ten perioperative factors were analysed as previously identified indices of subsequent mortality: age and sex, preoperative systolic blood pressure, haemoglobin, haematocrit, amylase, creatinine, platelet count and activated partial thromboplastin time (APTT), preoperative cardiac arrest, and the type of rupture (intra- or retroperitoneal). χ^2 test† or logistic regression analysis* was used to compare outcome variables.
Results: The 30-day mortality was 53 per cent. Intraperitoneal rupture was the greatest independent predictor of mortality (intraperitoneal 95 per cent, retroperitoneal 27 per cent; $P<0{\cdot}001$, OR 18·7)*. Other variables significantly associated with mortality included: preoperative coagulopathy (platelets $<100 \times 10^9$/l and APTT >60 s $P<0{\cdot}001$, OR 15·7)*, preoperative cardiac arrest ($P=0{\cdot}002$, OR 11·5)*, systolic blood pressure <91 mmHg ($P<0{\cdot}001$, OR 9·46)*, haemoglobin <8 g/dl ($P<0{\cdot}001$)†, haematocrit <25 per cent ($P<0{\cdot}001$)†, age >76 years ($P<0{\cdot}01$)†, and amylase >340 µ/l ($P<0{\cdot}005$)†.
Conclusion: In this series intraperitoneal rupture was the greatest predictor of early mortality. It should be reported in future series of emergency aneurysm surgery for the purposes of comparative audit.

Vascular 044

Endovascular abdominal aortic aneurysm repair attenuates the metabolic response associated with conventional surgery

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Background: Endovascular abdominal aortic aneurysm (AAA) repair has been proposed as a minimally invasive alternative to conventional surgery. This study aimed to quantify the metabolic response in comparative cohorts undergoing both conventional and endovascular aortic surgery.
Method: Forty-three patients were allocated to endovascular or conventional surgery according to aneurysm morphology. All patients received a standard general anaesthetic and had 17 serial blood (venous and mixed venous, via pulmonary artery catheter) and urine samples collected in the perioperative period. Blood samples were immediately centrifuged and plasma snap frozen in liquid nitrogen for later analysis. Samples underwent analysis for the cytokines, interleukin (IL)-1β, tumour necrosis factor-α (TNF-α) and IL-6. White cell and platelet activation were estimated indirectly by measuring L-selectin and myeloperoxidase and thromboxane β2 and 11-dehydrothromboxane β2 (11-dhTx), respectively. Renal injury was assessed by estimation of the albumin/creatinine ratio (A/C) and urinary NAGs. Fibrinogen and D-dimer were calculated to assess activation of the clotting cascade.
Results: Twenty-three patients underwent endovascular AAA repair. Their median age was 72 years (range 60–81 years) and aneurysm size 5·5 (range 4·8–7·3) cm. Twenty had conventional surgery. Their median age

was 67 (range 58–81) years and aneurysm size 5·7 (range 5·0–9·4) cm. All metabolites varied throughout the perioperative period. Results are illustrated as peak median values.

	IL-1β† (pg/ml)	TNF-α† (pg/ml)	IL-6† (pg/ml)	A/C‡ (mg/mmol)	D-Dimer	11-dhTx† (pg/ml)
Conventional	3·4	27·3	217·4	26·4	4500	1291·6
Endovascular	2·6*	11·0*	144·2*	13·2*	1250*	2918·2*

$^*P<0{\cdot}05$

Conclusion: These data suggest the ischaemia reperfusion injury associated with conventional aneurysm repair is largely negated by endovascular techniques. This may be translated to a lower incidence of multiple organ failure after endovascular surgery.

Vascular 045

Outcome for patients with large abdominal aortic aneurysms considered unfit for surgery

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Background: This study aimed to determine the risk of rupture in untreated large abdominal aortic aneurysms (AAA) and provide data to assist the decisions to operate, or not, in high-risk patients.
Method: Clinicians were asked to refer all patients found to have an AAA, even if unfit or elderly. In 9 years, 60 of 192 patients with an AAA 5 cm or greater were judged unfit for elective operation. Data were available for 58 non-operated patients with a minimum follow-up of 2 years. Initial AAA diameters at presentation were 5–5·9 cm ($n=25$) and ≥6 cm ($n=33$). Kaplan–Meier survival curves were calculated for both groups.
Results: Of 41 patients aged ≥80 years, 33 (80 per cent) were rejected for operation, compared with only 17 per cent of those patients aged <80 years. The reason for rejection was cardiovascular problems (26), 'old age' (15), malignancy (8), respiratory (6) and patient wishes (3). The mean age of non-operated patients was 80·7 (range 69–93) years. At the end of the study 51 out of 58 non-operated patients had died, with seven still alive. Median survival was 19 (range 1–99) months. The annual risk of rupture for a 5–5·9 cm AAA was 9 per cent, and for ≥6 cm AAA 13 per cent. The median time to rupture was 18 (range 1–38) months. Death from other causes occurred in 29 patients, compared with 19 deaths from rupture and three deaths of uncertain cause, two of them sudden. Three patients had operations for rupture with two deaths and one survivor. For the electively operated group of 132 patients (mean age 73 years) the 30-day mortality was four (3 per cent).
Conclusion: The minimum annual risk of rupture for an AAA >5 cm exceeds the expected operative mortality for fit patients. However, in the unfit group most died of other causes and few would have benefited from elective operation.

Vascular 046

Sac volume following endoluminal repair of aneurysms

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Background: What happens to the sac after endoluminal repair of an aneurysm remains uncertain. The aim of this study was to assess sac volume in the first 2 years after such repair.
Method: Twenty-eight cases of endoluminal repair of aneurysms, 21 infrarenal abdominal (AAA), three iliac and four popliteal, underwent 3-dimensional reconstruction of their computerized tomographic flow lines and proximal neck diameters over a median period of 11 months (range 6–22 months) were calculated.
Results: The analysis is shown below:

	Total sac volume (ml)	Volume of thrombus (ml)	Flow-line (mm)	Proximal neck diameter (mm)
Preoperative	119 (78–294)	38 (11–124)	86·1 (52·9–112·2)	20·3 (15·6–24·1)
Postoperative 5 days	133 (100–338)	76 (42–258)	80·1 (57·5–115·2)	21·4 (17·0–26·1)
Postoperative >6 months	128 (95–364)	82 (37–270)	89·4 (60·6–123·5)	21·0 (17·8–23·3)
P (Wilcoxon)	ns	Pre vs 5 days <0·05	<0·05	Pre vs 5 days <0·05

The changes in total sac volume became significant ($P<0{\cdot}05$) after two patients with obvious upper stent leaks were excluded. Perigraft flow in three other patients from patent lumbar arteries did not affect volume measurements. The linear changes in the flow line were reflected by similar changes in the vascular channel volumes through the aneurysm. The maximal anteroposterity diameter did not change significantly although the shape of the aneurysm did. Similar results were obtained from the iliac and popliteal aneurysms. There was no change in the distance between the lowest renal and the top of the upper stent over the period of the study.
Conclusion: There was a significant increase in sac volume 5 days after aneurysm exclusion due to an increase in thrombus volume followed by a <5 per cent decrease after 6 months. This was accompanied by an initial shortening of the flow line at 5 days, followed by a 4 per cent increase after a median of 11 months implying lengthening of the graft. Proximal neck diameter initially increased and then did not change, and there was no slippage of the stent-graft.

Vascular 047

Abdominal aortic aneurysm repair in octogenarians

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Background: This study aimed to determine perioperative morbidity and mortality in octogenarians undergoing abdominal aortic aneurysm (AAA) repair and to identify the factors that influence early survival.
Method: Retrospective case note review of 77 octogenarians (60 men, 17 women), median age 82 (range 80–91) years undergoing AAA repair between 1979 and 1994. There were 25 elective, 14 symptomatic, and 38 ruptured AAAs in the series. Mean aneurysm diameter was 72 (range 50–120) mm. Forty-one of the 77 patients (53 per cent) had a preoperative history of cardiac, respiratory, renal or cerebrovascular disease. Thirteen (17 per cent) had a history of disease affecting two of these systems.
Results: Overall 30-day mortality in the series was 47 per cent (36 of 77). Thirty-day mortality in the elective group was 20 per cent (5 of 25), in the symptomatic group 36 per cent (5 of 14) and in the ruptured group 68 per cent (26 of 38) ($P<0{\cdot}001$, χ^2 test). Perioperative complications occurred in 50 of 77 (65 per cent) patients. These included pneumonia in 22 (29 per cent), myocardial infarction in 32 (42 per cent), renal failure in 11 (14 per cent) and multi-system organ failure in 6 (8 per cent) patients. Preoperative comorbidity, AAA size and type of graft used for repair did not influence survival. Type of AAA (elective, symptomatic or ruptured) was the only independent predictor of survival in these patients.
Conclusion: Perioperative morbidity and mortality in octogenarians undergoing AAA repair in this series is high, including the elective patient subgroup. Rigorous patient selection is necessary when considering octogenarian patients for AAA repair.

Vascular 048

Centralized vascular surgical services and the community outcome for ruptured abdominal aortic aneurysm

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Background: The aim of this study was to examine the community management of patients with ruptured abdominal aortic aneurysm (AAA) within the catchment area of this regional vascular surgery unit and to examine the relationship between transfer distance and outcome in patients admitted to this unit.
Method: Population data for the catchment area were obtained from the Information and Statistics Division of the National Health Service. Unit data were obtained from a prospectively gathered database. Transfer distance was defined as the road distance between this unit and the patient's residence.
Results: Between 1 January 1989 and 31 December 1995, 972 cases of ruptured AAA were identified. Two hundred and nineteen (23 per cent) patients were certified dead in the community; 372 (38 per cent) patients were admitted to hospital but not transferred to this unit, and of these only 24 were operated and 14 survived. Of the 381 (39 per cent) patients admitted to this unit, overall mortality was 152 of 310 (49 per cent) patients who were admitted directly and 41 of 71 (58 per cent) patients who were transferred from other hospitals. Operated patients ($n = 316$, 83 per cent) travelled significantly further (median 6·9, range <1–39, miles) than 65 (17 per cent) non-operated patients (median 3·1, range <1–36, miles, $P = 0{\cdot}0001$, Mann–Whitney). There was no significant difference in transfer distance between 188 (59 per cent) operated patients who survived (median 5·5, range <1–31, miles) and 128 (41 per cent) who did not (median 5·5, range <1–29, miles $P = 0{\cdot}9$). Overall community survival from ruptured AAA was 202 of 972 (20 per cent).
Conclusion: These data suggest that transferring stable patients with ruptured AAA to a regional vascular unit does not increase operative mortality. Whether the need to transfer patients reduces the proportion who are deemed appropriate for surgical intervention so prejudicing community mortality remains unknown.

Vascular 049

Ruptured abdominal aortic aneurysm is associated with inhibition of systemic fibrinolysis

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Background: It has been suggested that ruptured abdominal aortic aneurysm (AAA) is associated with systemic fibrinolysis and that haemorrhage may be limited by anti-fibrinolytic therapy with aprotinin. This study examines systemic fibrinolysis and thrombin generation in patients operated for ruptured and non-ruptured AAA.
Method: Ten patients undergoing emergency repair of ruptured and nine undergoing repair of non-ruptured AAA were studied. Tissue plasminogen activator (t-PA) activity, plasminogen activator inhibitor (PAI) activity, and prothrombin fragment (PF) 1+2 were measured preoperatively, immediately before and 5 min after aortic clamp release, and 24 h postoperatively.
Results: Preoperatively, ruptured AAA was associated with significantly increased PAI activity (median 36·5, range 20·6–38·8 activity units/ml) versus non-rupture (median 8·2, range 3·2–21·7; $P < 0{\cdot}001$, Mann–Whitney) and significantly decreased t-PA activity (median 0·12, range 0·06–0·43 IU/ml) versus non-rupture (median 0·49, range 0·14–3·2; $P < 0{\cdot}01$, Mann–Whitney). In both groups there was a significant increase in PF 1+2 above the normal range (0·4–1·1 nmol/l) but this was significantly greater in patients with rupture (median 9·0, range 5·4–11·6) versus non-rupture (median 2·2, range 0·7–7·1; $P < 0{\cdot}001$, Mann–Whitney). These differences persisted throughout the course of surgery. At 24 h, PAI activity remained above normal for ruptured AAA but was not significantly different from non-rupture; t-PA activity was within the normal range in both groups, and PF 1+2 remained above the normal range in both groups but there was no significant difference between the groups.
Conclusion: Ruptured AAA is associated with systemic thrombin generation and inhibition of systemic fibrinolysis. These data do not support the use of anti-fibrinolytic therapy in patients operated for ruptured AAA.

Vascular 050

Training in abdominal aortic aneurysm surgery

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Background: Reduction in working hours and 'Calmanization' of training mean that operative experience must be gained more quickly. This study examines the effect of Calman on training and outcome after abdominal aortic aneurysm (AAA) repair, a nationally agreed vascular 'indicator operation' (Royal College Confidential Enquiry into Surgical Training 1996).
Method: Analysis of a prospectively gathered computerized database of 1116 consecutive AAA repairs performed between 1 January 1987 and 30 September 1997.
Results: Since 1991, supervised trainees have performed a significantly greater proportion of both elective and emergency cases ($P < 0{\cdot}01$, χ^2 test). Overall operative mortality did not differ significantly between the two time periods studied, and within each time period mortality was not significantly related to consultant presence at the operating table (Table).

		1987–1991	1992–1997
Elective	Consultant operating/assisting/not scrubbed (*n*, %) operative mortality (%)	95(73)/26(20)/9(7) 5(5)/3(8)/0	129(55)/79(33)/28(12) 7(5)/7(9)/2(7)
Symptomatic	Consultant operating/assisting/not scrubbed (*n*, %) operative mortality (%)	84(69)/23(19)/14(12) 6(7)/3(13)/1(7)	68(49)/36(26)/35(25) 9(13)/3(8)/3(9)
Rupture	Consultant operating/assisting/not scrubbed (*n*, %) operative mortality (%)	173(76)/36(16)/20(8) 67(39)/10(28)/4(20)	155(59)/47(18)/59(23) 66(43)/12(26)/30(51)

Conclusion: Supervised trainees can perform an increasing proportion of elective and emergency AAA surgery without increasing operative mortality. Towards the end of training, surgical trainees can safely operate 'solo' in selected cases.

Vascular 051

Percutaneous endoluminal grafting for femoropopliteal disease: a feasibility study

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Background: A feasibility study was carried out to assess the role of a balloon-mounted expanded polytetrafluoroethylene graft with proximal and distal anchoring stents in patients with disabling claudication considered unsuitable for angioplasty because of the severity of the disease.

Method: Thirty-one patients with claudication were considered suitable for treatment. All had significant disease confined to the superficial femoral artery (SFA) and satisfied the entry criteria of two or more vessel run-off and minimum SFA diameter of 4 mm at stent anchor sites. Six were subsequently excluded following intravascular ultrasound interrogation. Procedures were performed under local (21) or general (4) anaesthesia, using a 9F introducer sheath.
Results: Successful deployment of the stent grafts was achieved in 22 cases, with three failures; two failures occurred after encountering difficulties with the introducer sheath and there was one device failure. Of those patients in whom graft deployment was successful, primary patency was achieved in ten (46 per cent) and secondary patency in 14 (64 per cent) at 1 year follow-up.
Conclusion: While initial results with this device have proved disappointing, current development in the design of this stent graft to one that is fully supported may result in this becoming a viable alternative to angioplasty or surgery.

Vascular 052

Colonoscopy with biopsy after aortic surgery: a unique study of the incidence of colonic ischaemia

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Background: Colonic ischaemia is a well-documented complication of abdominal aortic reconstruction. This is the first prospective study in which all patients have had routine pre- and postoperative colonoscopy and biopsy, in order to determine the true incidence and implications.
Method: Fifty-six patients undergoing elective infrarenal aortic surgery, 28 for aneurysm and 28 for occlusive disease, were colonoscoped and biopsied preoperatively and 1 week postoperatively.
Results: All patients had normal macroscopic and microscopic appearances on preoperative biopsies. A 30 per cent incidence of postoperative colonic ischaemia was identified by histology (16 of 53 patients), almost half of these (7 of 16) having normal macroscopic appearances. Two factors exhibited a statistically significant association with the development of ischaemia: prolonged cross-clamp time (mean of 44·75 versus 35 min, $P<0·05$, Mann–Whitney U test) and postoperative diarrhoea (88 per cent versus 13 per cent, $P<0·001$, Fischer's exact test). Co-morbidity was much higher in those patients with ischaemia (81 per cent versus 13 per cent, $P<0·005$, Fisher's exact test). Overall morbidity was significantly greater in the aneurysm group (46 per cent versus 21 per cent, $P<0·05$, Fisher's exact test).
Conclusion: Colonic ischaemia after aortic reconstruction is a much more commoner occurrence than previously reported and, although mild and transient in many cases, is still associated with significant morbidity. When suspected, colonoscopy with biopsy is recommended.

Vascular 053

Intravenous clot versus thrombus: serious implications of conclusions drawn from studies using models of 'thrombosis'

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Background: Many models of thrombosis exist but adequate characterization of the coagulum produced has often not been performed. In some models, isolated venous segments have been used and in others, blood flow is completely stopped which by definition may not result in true thrombus formation. This study aimed to determine whether the histological and electron microscopic appearances of human venous thrombus, experimental intravascular 'thrombus' formed in isolated vein segments, experimental thrombus formed in flowing blood and *ex vivo* clot are similar in structure and composition.
Method: Two rat models of thrombosis were used. One model used diminished flow only. The other used an isolated segment with no flow. Human thrombi were obtained from deep veins in amputation specimens and superficial veins from varicose vein operations. Human and rat clots were formed from peripheral blood. Paraffin sections were stained with Martius Scarlet Blue, haematoxylin and eosin, and immunocytochemical stains for leucocytes, platelets, fibrin and monocytes. Specimens for electron microscopy were either perfuse-fixed or post-fixed in glutaraldehyde.
Results: Human thrombus had an organized structure comprised of alternate layers of platelet/fibrin and red cells. White cells lined up along these layers. The thrombus from the rat model using low flow only was identical to human thrombi. The *ex vivo* clots were similar to each other, being comprised almost exclusively of red cells with randomly distributed white cells and very few platelets. Fibrin was present only as clumps. Thrombi from the no-flow model closely resembled the *ex vivo* clots. Scanning electron micrographs revealed that the colts and 'thrombi' produced in no-flow segments consisted largely of red cells trapped within a loose mesh of fibrin. Platelets were more abundant in human thrombus and the low-flow model.
Conclusion: Thrombus produced in a model where flow is reduced, without complete occlusion, is similar to human thrombus but both are markedly different in structural formation from *ex vivo* clots and the coagulum produced by some thrombosis models. Resolution of these different tissues, therefore, may also be dissimilar and thus, conclusions drawn about the effectiveness of substances intended to inhibit thrombogenesis or accelerate thrombolysis may be invalid when experimental models using cessation of flow are employed.

Vascular 054

Outcome following abdominal aortic aneurysm surgery in a district general hospital

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Background: The aim of this study was to assess the survival of patients undergoing elective and emergency abdominal aortic aneurysm (AAA) surgery in a district general hospital.
Method: A retrospective review of accident and emergency, operating theatre, intensive care unit and ward documentation revealed that, from 1 January 1986 to 31 March 1997, 118 patients underwent AAA surgery in this hospital. Individual patient details were obtained from the case notes. Fifty-two patients underwent elective repair: 42 men and 10 women of median age 70 (range 52–82) years. Sixty-six patients underwent emergency repair; 58 men and eight women of median age 70 (range 45–85) years.
Results:

Interval (months)	No. patients at risk at start	Patients withdrawn due to: Duration	LFU	Death	Interval survival	Cumulative survival (%)	Standard error (%)
0–1	*52* **66**	*0* **0**	*0* **0**	*1* **19**	*0·98* **0·71**	*100* **100**	*0* **0**
1–3	*51* **47**	*0* **0**	*1* **6**	*0* **7**	*0·98* **0·98**	*98* **71**	*1·94* **5·58**
3–12	*50* **40**	*9* **7**	*2* **2**	*1* **4**	*0·98* **0·97**	*96* **70**	*2·27* **6·06**
12–24	*38* **27**	*3* **1**	*5* **3**	*0* **7**	*1·00* **0·72**	*94* **68**	*3·74* **7·40**
24–48	*30* **16**	*1* **1**	*2* **2**	*2* **6**	*0·96* **0·59**	*94* **49**	*4·20* **8·75**
48–60	*25* **7**	*7* **1**	*5* **0**	*1* **0**	*0·95* **1·00**	*90* **29**	*5·69* **9·24**
60–72	*12* **6**	*4* **3**	*0* **0**	*1* **1**	*0·90* **0·75**	*86* **29**	*9·29* **9·98**
72–84	*7* **5**	*2* **0**	*0* **0**	*3* **1**	*0·50* **0·80**	*77* **22**	*13·96* **8·69**

Emergency AAA in **bold**, elective AAA in *italics*. LFU = lost to follow-up.

Conclusion: Acceptable 30-day mortality can be obtained in a district general hospital for both elective and emergency AAA repair. Long-term survival following emergency surgery is much lower than that for elective, and this may have implications regarding AAA screening.

Vascular 055

An audit of varicose vein surgery: the patient's perspective and the reasons for dissatisfaction

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Background: Variscose veins (VVs) are common and constitute a significant workload in surgical practice. We have tried to elicit patient satisfaction after VV surgery and to determine the causes of dissatisfaction.
Method: A questionnaire was sent to 404 patients who had undergone VV surgery over a 2-year period, requesting information about symptoms before and after surgery, postoperative complications and satisfaction following operation. These results were correlated with information obtained from theatre registers and patient case notes.
Results: Three hundred and thirty-five patients responded. The main symptoms were aching (59 per cent), itching (33 per cent), acute pain (24 per cent) and ulcers (7 per cent). Postoperative complications were reported by 36 per cent (bruising 58 per cent, infection 26 per cent, bleeding 18 per cent, others 23 per cent). Seventy-nine per cent were satisfied with the outcome of surgery and 88 per cent noted an improvement in symptoms. Ninety-five per cent were satisfied with the preoperative explanation. The main factors associated with dissatisfaction were being female (24 per cent versus 11 per cent; $P<0{\cdot}025$), bilateral surgery (32 per cent; $P<0{\cdot}02$), junior staff performing the operation (31 per cent versus 18 per cent; $P<0{\cdot}025$), postoperative complications (29 per cent; $P<0{\cdot}005$), no improvement in symptoms (75 per cent; $P<0{\cdot}005$) and dissatisfaction with preoperative explanation (61 per cent; $P<0{\cdot}0005$). Although dissatisfied with the results of surgery, 57 per cent reported an improvement in symptoms. Of the 69 non-responders, 41 were reviewed in the out-patient clinic and 85 per cent were satisfied.
Conclusion: The vast majority of patients were satisfied and benefitted from the VV operation. Satisfaction rates may be further improved by ensuring that the patient is fully informed about the operation and its limitations, and that junior staff are better trained and supervised in operating on VVs.

Posters 1–116

Breast

Poster 001

Immunohistochemical expression of Desmoglein 2 and E-cadherin in breast carcinomas relative to other known prognostic factors

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Background: This study aimed to compare the relative immunohistochemical (IHC) staining of two cell–cell adhesion molecules, Desmoglein 2 (Dsg2) and E-cadherin (E-cad), in breast cancer and normal breast tissue. Correlation of this staining with several known clinical and IHC prognostic factors was also studied.
Method: Frozen tissue from 52 ductal, 11 lobular, three ductal carcinomas *in situ* (DCIS), 11 tumour-associated normal (TAN) and nine normal breast tissues were IHC stained using Dsg2 and E-cad monoclonal antibodies.
Results: Both antibodies demonstrated membranous staining in the majority of carcinomas (98 per cent versus 80 per cent, Dsg2 versus E-cad, respectively). Significantly stronger IHC staining was seen in normal compared to carcinoma ($P<0.0001$) with both antibodies, and between DCIS and carcinoma ($P=0.02$ and $P=0.07$, E-cad versus Dsg2, respectively). There was an inverse correlation in IHC staining and size of the primary tumour which reached significance with E-cad ($P=0.04$ versus $P=0.07$, E-cad versus Dsg2, Mann–Whitney U-test). E-cad showed an inverse correlation with grade of ductal tumour ($P=0.04$, Grade 1 demonstrating strong membranous staining versus Grade 2 and 3). There was a trend for lobular carcinomas to stain weakly with both antibodies when compared with the ductals and this was significant with E-cad ($P=0.004$ versus $P=0.059$, E-cad versus Dsg2, respectively) No relationship was seen with lymph node status or any of the remaining prognostic factors examined.
Conclusion: We have demonstrated that Dsg2 and E-cadherin are present in breast cancer tissue and that both cell–cell adhesion molecules may be important in the local progression of breast cancer

Poster 002

Prognostic significance of CD44s and CD44v6 in breast cancer, an immunohistological study

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Background: A number of studies *in vitro* and *in vivo* have associated the expression of the v6 variant isoform of CD44 with an increased incidence of metastasis We examined the prognostic significance of CD44v6 in a group of 109 women with stage 2 breast cancer
Method: This study, using immunohistochemical techniques, examined the prognostic significance of CD44s and CD44v6 expression in a cohort of 109 women with a median follow-up of 50 months, presenting with stage 2 breast cancer
Results: CD44v6 expression in tissue sections was found to be independent of patient age, tumour size and grade, and lymph node status. Neither was any correlation established between CD44v6 expression, and serum levels of Ca153 both pre- and postoperatively, BCL2, nm23, p53, P cadherin, or oestrogen receptor status. Similar findings were observed for CD44s. A significant correlation was observed between expression of CD44s and CD44v6 ($P<0.05$ χ^2). Overall and disease-free survival were both found to be independent of expression of CD44s and/or CD44v6
Conclusion: In conclusion, CD44s and CD44v6 expression did not correlate with established prognostic indicators, disease-free survival, overall survival, or tumour differentiation

Poster 003

MRI in the detection of breast cancer multicentricity

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Background: Whilst mammograms rely on microcalcifications for detecting cancers, contrast-enhanced magnetic resonance imaging (MRI) relies on vascularity and vascular permeability. In this study we compared the preoperative detection of multicentric foci (MCF) by contrast-enhanced MRI with standard radiological-histological examination of resected specimens (modified Egan's method).
Method: Ten patients with newly diagnosed breast cancer underwent preoperative contrast-enhanced breast MRI using a transverse T1-weighted three-dimensional (3D) FLASH sequence. After surgical excision the specimens were fixed and cut in the same plane as the MRI. The pathologist sampled any identifiable lesion for histological analysis and subsequently a radiograph was performed on the specimen slices Two observers identified calcifications away from the primary tumour and these were then sampled and paraffin blocked. One section was cut from each block, stained and examined by microscopy The remaining blocks were X-rayed and further sections were taken if calcifications were identified. MRI images were reviewed independently and findings compared with histology.
Results: On radiography of tumour slices, 71 suspicious areas were identified and sampled Out of these, 15 areas of DCIS or invasive cancer were identified in five patients On MRI, 19 enhancing foci were identified in seven patients. All five patients with histologically proven malignant areas had some enhancing foci on MRI Two tumours showed diffuse patchy enhancement and in these all 11 areas sampled showed either DCIS or frank invasive disease MRI could potentially detect 14/15 histologically proven MCF (false positive = 1) but detected four additional enhancing foci (false positive = 4).
Conclusion: Our findings suggest that MRI is highly sensitive for the detection of MCF invasive or *in situ* tumours but that the specificity for the diagnosis of malignant change in these foci may be low MRI could be used to investigate the clinical significance of unresected MCF in a future prospective study

Poster 004

Sentinel lymph node biopsy in breast cancer: prospective assessment of two complementary techniques

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Background: Axillary lymph node dissection is a necessary staging procedure in breast cancer but is associated with potentially avoidable morbidity in patients with node-negative disease. The aim of this study is to assess two complementary methods of sentinel node assessment in patients with early breast cancer.
Method: Sentinel node localization was performed using 45 mbi of tech-

netium-labelled sulphacolloid injected subdermally close to the tumour 4–6 h prior to surgery. All patients underwent lymphoscintigraphy prior to surgery. In addition 1·5 ml of patent blue dye was injected peritumourally at the time of surgery following the induction of anaesthesia and prior to skin preparation. An axillary clearance was then performed after location of the sentinel node by a combination of direct visual identification of blue dye and directional gamma detector (Neoprobe, Autosuture, UK).
Results: A consecutive initial series of 15 patients have been recruited for the study. The sentinel node (node with the highest level of counts or concentration of blue dye) was successfully identified in all cases by the Neoprobe and was visibly blue in 10 of the 15 patients. Five patients had node-positive disease and in all five the sentinel node was positive (in three it was the only positive node). Blue dye identified the positive node in three of the five cases.
Conclusion: These preliminary results demonstrate that the two techniques are complementary but the Neoprobe appears to be the more sensitive technique. Application of this technique should facilitate the utilization of less radical axillary surgery in the majority of patients with early breast cancer.

Poster 005

Assessment of mammographic abnormalities with the Advanced Breast Biopsy Instrumentation system

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Background: The drawbacks of breast screening include unnecessary intervention in patients with benign disease and lack of preoperative diagnosis in patients with screen-detected malignancy. We are prospectively assessing the impact of the Advanced Breast Biopsy Instrumentation (ABBI) system (Autosuture U.K.) which allows stereotactic biopsy and excision of screen-detected lesions.
Method: Patients with screen-detected clinically occult abnormalities were referred for evaluation on the ABBI system. All procedures were carried out under local anaesthetic. All data including a patient satisfaction questionnaire were collected prospectively by a dedicated research nurse.
Results: To date, 78 patients have undergone 20 excision biopsies and 58 core biopsies. Of the excision biopsies, 10 were malignant: six invasive ductal, four ductal carcinoma *in situ*, and the remaining benign lesions included radial scars ($n = 2$), complex sclerosing lesions ($n = 2$) and fibroadenomata. Mean duration of the excision biopsies was 50 (range 30–105) min. Histology of the core biopsies revealed malignancy in 12 cases and benign disease in 46. The procedures were well tolerated by all patients with no complications.
Conclusion: The ABBI system provides a well-tolerated accurate diagnostic intervention for patients with screen-detected breast lesions. It facilitates accurate preoperative diagnosis and has the potential for therapeutic applications in patients with very small radiologically detected cancers.

Poster 006

Will routine breast screening improve mortality?

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Background: Screening mammography aims to detect disease at an earlier stage in the belief that earlier surgery will cure more women. We analyse the impact of the NHS screening programme on disease stage and incidence rates, and provide an assessement of whether the desired reduction in mortality is likely to be achieved.
Method: All cases of invasive breast cancer from 1982 to 1996 in women under 75 who lived in a defined geographical area served by two screening centres were identified and the pathology reports obtained. The incidence rates for the second round were adjusted to pre-screening levels and the 7-year mortality estimated.
Results: A significant stage migration was seen and more crucially a reduction in the incidence of large tumours (Table). Our estimate of the 7-year mortality reduction due to screening was approximately 20 per cent.

Table: the incidence of breast cancer in women aged 50–64 by screening round and the expected mortality benefits.

Tumour size	7-year mortality	Incidence pre-screening (per 100 000)	Adjusted incidence interval round	Mortality rate pre-screening (per 100 000)	Estimated mortality by first interval	Estimated benefit
<20 mm	17%	36·8	78·2	6·3	13·3	–7·0
20–39 mm	36%	55·0	39·7	19·8	14·3	5·5
>40 mm	55%	22·7	10·6	12·5	5·8	6·2
Not stated	45%	38·2	24·4	17·2	11·0	17·2
Total		152·7	152·9	55·8	44·4	12·85

Conclusion: The NHS Breast Screening Programme has lowered the incidence of large tumours. This decrease should translate into a 20 per cent reduction in mortality in the next few years.

Poster 007

Definitive axillary treatment and survival of node-positive women with breast cancer

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Background: There remains much debate on the necessity and extent of axillary dissection in the surgical management of breast cancer and whether axillary recurrence is associated with a poorer overall survival. The aim of this study is to investigate the impact of inadequate definitive treatment of the axilla, with either surgical clearance or radiotherapy on the survival of node-positive women.
Method: A total of 7144 women with histologically confirmed invasive breast cancers, aged <75 years, who lived in a defined geographical area (population 1·5 million) were identified through the cancer registry between 1980 and 1994. Details of treatment were derived from case records and pathology reports. Cause of death was derived from death certificate data.
Results: Four hundred and eighteen node-positive women had less than four nodes sampled. These women had a significantly poorer survival compared to women with four or more nodes sampled, $P = 0·0017$ (see Table). On reviewing the case-notes of the women with less than four nodes removed only 14 per cent (5/36) were referred for radiotherapy in 1980 but this had risen to 65 per cent (22/34) by 1992–1994.

Table: the 5- and 10-year survival and relative hazard ratio (RHR) of node-positive women by sample size.

	Axillary node sample size	
	<4 nodes	>4 nodes
Number of patients	418	1809
5-year survival	53	59
10-year survival	34	42
RHR*	1·26 (1·092–1·464)	1·0

*RHR: The relative hazard ratio adjusted for tumour size

Conclusion: Adequate axillary treatment remains necessary for regional disease control and survival. The majority of node-positive women with less than four nodes removed were not referred for radiotherapy and this may have contributed to the poorer survival of these patients.

Poster 008

The value of potential markers of angiogenesis in breast cancer

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Background: Production of the potent endothelial cell mitogen vascular endothelial growth factor (VEGF) correlates, in breast cancer cytosols, with development of angiogenesis (assessed by microvessel density) and induces vascular cell adhesion molecule (VCAM) expression in endothelial cells. The aim of this study was to assess the value of serum VCAM and VEGF in predicting tumour angiogenesis and metastasis as well as assessing response to therapy.
Method: Serum levels of soluble VCAM and VEGF were measured in women with early breast cancer (EBC) ($n=93$) and women with progressing advanced breast cancer (ABC) ($n=24$) using ELISA (R&D Systems Ltd., Oxon, UK). Serum measurements were compared to known histological prognostic parameters and to microvessel density by immunostaining tumours with the CD31 antigen.
Results: In EBC serum levels of VCAM (mean 769·5, range 263–1387, ng/ml) were higher than both pre- and postmenopausal controls (483 ng/ml and 478 ng/ml, $P<0·001$ and $P<0·01$, respectively). Levels of serum VEGF in EBC (mean 299 ng/ml, range 47·1–1321) were raised only when compared to postmenopausal women (mean 246, range 66·5– 621·5, ng/ml) ($P<0·05$). Levels of serum VCAM, but not VEGF, correlated with microvessel density ($r=0·66$, $P<0·001$). Serum VCAM, but not VEGF, was raised in women with ABC (mean 1236, range 349–3914) when compared to EBC ($P<0·001$) and normal controls.
Conclusion: Serum VCAM is a sensitive marker of angiogenesis in breast cancer that could be used to assess responses to therapy in women with ABC and may have prognostic value in EBC. Measurement of serum VEGF levels does not provide diagnostic or prognostically valuable clinical information.

Poster 009

Body mass index, height and cumulative menstrual cycles are not risk factors for poor outcome in breast cancer

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Background: The aim of this study was to determine whether body mass index, height and cumulative menstrual cycles are independent prognostic factors following the diagnosis of primary breast cancer.
Method: The body mass index (BMI), height and cumulative menstrual years were calculated at the time of diagnosis for 448 women with primary breast cancer. The effect of BMI, height and cumulative menstrual years on survival time and disease-free interval was estimated by fitting a Cox regression model in each case with all three variables as continuous covariates (significance assessed by likelihood ratio tests).
Results: BMI and height were calculated for $n=403$ patients and cumulative menstrual cycles in $n=388$; there was no effect of BMI on survival time ($P=0·99$; hazard ratio = 1000 [95 per cent confidence interval {CI} range 0·968–1·034]) or disease-free interval ($P=0·92$; hazard ratio = 1·002 [95 per cent CI, range 0·973–1·031]). Height did not affect survival ($P=0·11$; hazard ratio = 0·137 [95 per cent CI, range 0·012–1·5 4]) or disease-free interval ($P=0·13$; hazard ratio = 0·180 [95 per cent CI, range 0·020–1·604]). Similarly, cumulative menstrual cycles did not influence survival ($P=0·74$; hazard ratio = 0·994 [95 per cent CI, range 0·961–1·028]) or disease-free interval ($P=0·34$; hazard ratio = 0·985 [95 per cent CI, range 0·955–1·016]).
Conclusion: The present study found no association between BMI, height and cumulative menstrual cycles on survival time or disease-free interval in patients with primary breast cancer.

Poster 010

Fish-tail plasty as a method of treating post-mastectomy dog-ear

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Background: Dog-ear at the lateral end of a mastectomy wound is a common problem, especially in obese patients where mastectomy frequently leaves behind excess skin at the lower border of the axilla. Although an apparently minor problem it often causes the patient great discomfort, the fold of skin rubbing against or overhanging the side panel of the bra. As there is a large fold of skin in this area simply excising the dog-ear may result in an inability to close the wound or may produce a dog-ear more posteriorly. We describe a simple technique for excising this fold at the time of mastectomy or as a secondary procedure.
Method: Under general anaesthetic the patient is positioned on her side with the arm on the affected side placed above her head. A W–Y plasty is performed; the skin is marked in the shape of a 'fish-tail' and the 'fish-tail' excised with either knife or diathermy; caution is taken not to undermine and remove fat from the triangle of skin left behind. The resulting Y is then sutured using 3·0 vicryl. We have treated 20 patients using this technique, five as a primary procedure during mastectomy and 15 as a secondary procedure.
Results: In all 20 patients we have prevented or eliminated the dog-ear at the lateral end of the mastectomy wound. One obese patient developed a wound infection when the procedure was performed as part of the mastectomy but there have been no other complications and all patients have been extremely satisfied with the result.
Conclusion: We conclude that the 'fish-tail' plasty is a successful method of treating post-mastectomy dog-ear as either a primary or secondary procedure.

Poster 011

Tumour bed positivity in women undergoing breast-conserving surgery for primary breast cancer

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Background: Local recurrence after breast-conserving surgery is associated with a short distant disease-free survival. Early local recurrence is caused by residual disease left behind at the time of initial surgery. The aims of this study were to define the incidence of incomplete excision by using a simple method of assessing residual disease in the tumour bed and to correlate tumour bed positivity with clinico-pathological variables and outcome measures.
Method: A total of 533 women with primary operable breast cancer entered the study between January 1988 and December 1995. Following wide local excision, a 'shaving' of the residual cavity wall was obtained and sent separately for histopathology. These were blocked extensively and sectioned serially and the type and extent of disease assessed. A total of 466 patients (86 per cent) underwent axillary clearance, 129 (28 per cent) of whom were node positive. In all, 398 (75 per cent) received adjuvant radiotherapy to the breast, 63 (12 per cent) chemotherapy and 424 (80 per cent) Tamoxifen.
Results: One hundred and ninety-four patients (36 per cent) had disease (*in situ* or invasive) in the tumour bed. Based on tumour bed positivity, 137 patients (26 per cent overall) either had a further re-excision or mastectomy. The mean follow-up was 6·1 years (range 1·1–8·8 years). Tumour bed positivity was significantly associated with younger age, smaller lumpectomy diameter, Bloom and Richardson grade II, lymph node positivity and the presence of lymphovascular invasion or extensive ductal carcinoma *in situ*. Tumour bed positivity was an independent predictor of systemic recurrence and breast cancer-related death. The local recurrence rate was 2 per cent, systemic recurrence rate 9 per cent and breast cancer-related death rate 7 per cent.

Conclusion: Tumour bed assessment by analysing a shaving of the residual cavity is a simple method of identifying residual disease and by adopting a selective re-excision policy, a low local recurrence rate can be achieved. Tumour bed positivity also appears to predict for systemic recurrence and poorer survival.

Poster 012

Intraoperative frozen section of axillary nodes: a study of its accuracy

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Background: The aim of this study was to assess the role of intraoperative frozen section.
Method: A selected group of 88 patients who either had a low probability of axillary node involvement or where attempts were being made to avoid an axillary clearance. All had a four-node axillary node sampling procedure and the four nodes assessed by frozen section.
Results: The results are shown in the Table. Three hundred and sixty nodes were examined by frozen section.

		Final histology	
	No. patients	Nodes positive	Nodes negative
Patients with negative nodes on frozen section	69	7	62
Patients with positive nodes on frozen section	26	26	0

Sensitivity = 73 per cent, negative predictive value = 90 per cent.

Conclusion: This study showed 10 per cent of patients whose nodes are negative on frozen section have involved nodes on paraffin section. Frozen section of node sampling or sentinel node biopsies has a significant failure rate.

Poster 013

Angiotensin receptor expression and prognostic significance in breast cancer

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Background: Angiotensin II (AII) is a biologically active peptide of the renin angiotensin system. Most of the known physiological actions of AII are mediated via its type I (ATI) receptor. AII regulates growth and development of tissues and thus may be an important factor in tumour progression. Using a specific monoclonal antibody we have previously shown ATI receptor expression in breast tissue. The aim of this study was to extend our data and relate the expression of ATI receptor to disease progression and to determine quantitatively its relationship to factors known to have prognostic significance in breast cancer.
Method: Formalin-fixed paraffin-embedded breast tissue sections from 151 women, aged between 22 and 84 years were examined by immunocytochemistry using the 6313G2 monoclonal antibody to the ATI receptor. A semi-quantitative staining intensity index (SII) was used to determine the level of expression of the ATI receptor.
Results: Breast tissue from 151 patients were examined, breast cancers $n=102$ (67·5 per cent), benign breast disease $n=47$ (32·5 per cent). Of the breast cancers 37 (36·3 per cent) patients had metastatic axillary lymph node involvement. Semi-quantitative analysis of the ATI receptor expression by SII revealed a range of 0·25–2·25. The mean score for receptor expression was higher in benign as compared to malignant breast tissue, but this difference did not reach significance ($P<0{\cdot}06$). Analysis of the receptor expression in breast cancer showed no relationship with tumour grade but was shown to be significantly correlated with lymph node involvement ($P<0{\cdot}03$).
Conclusion: The expression of ATI receptor appears to be higher in benign as compared to malignant breast tissue. Patients with axillary nodal involvement show a reduction in receptor expression compared to node-negative patients, suggesting AII may be involved in breast cancer metastasis.

Poster 014

Beware the clear margin after breast conserving surgery

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Background: This study aimed to assess the role of cavity biopsies in assessing the adequacy of clearance after a wide local excision (WLE) for breast carcinoma.
Method: Data were collected prospectively over a 6-year period. Patients undergoing a WLE for invasive cancer ($n=153$), with ductal carcinoma *in situ* (DCIS) ($n=91$) and without DCIS ($n=62$) had biopsies taken from the superior, inferior, medial and lateral flaps together with a deep fascial biopsy. WLE specimens were inked and the margins examined rigorously by the orange peel method. Cavity biopsies were examined in their entirety.
Results:

	Margins clear	Margins involved
Cavity clear	65 (57)	11 (2)
Cavity involved	10 (1)	5 (2)

Figures in brackets are of tumours not associated with DCIS.

When the main specimen contained DCIS 10 per cent of cases had a clear margin with an involved cavity compared to 3 per cent without DCIS ($\chi^2=10{\cdot}28$, $0{\cdot}02>P>0{\cdot}01$).
Conclusion: There is a significantly greater chance of residual disease if invasive tumour is associated with DCIS, and cavity biopsies should not be used in isolation to assess clearance.

Poster 015

Can colour Doppler ultrasonography influence decision on surgical management of the axilla in breast cancer patients?

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Background: Axillary dissection is essential in the treatment of breast cancer patients but up to 70 per cent of patients will be negative for nodal metastases and at present no methods are totally accurate for preoperative assessment of nodal status to avoid unnecessary morbidity associated with axillary surgery. Axillary lymph node imaging by colour Doppler ultrasonography (CDU) has a reported accuracy of up to 86·4 per cent and may allow a more appropriate selection of patients for either axillary sampling or clearance.
Method: We have studied a total of 123 patients prospectively and the breast and axilla were scanned with CDU before surgery (age range 26–82 years). One hundred and twenty had unilateral operable breast cancer, two had bilateral cancers and three had axillary recurrences. Patients with large tumours (T3 and T4), clinically involved axillary nodes or positive flow signal on CDU were selected for axillary clearance. All other patients had level 1 axillary sampling.
Results: CDU has a sensitivity of 68 per cent, specificity of 85·33 per cent and positive predictive value of 75·56 per cent. Out of 50 patients with involved nodes 16 had false-negative axillary scans and were treated with radiotherapy to the axilla following axillary sampling. Eleven out of

75 patients with negative nodal metastasis had false-positive scans and underwent axillary clearance, but 85·33 per cent (64/75) of these node-negative patients avoided axillary clearance.
Conclusion: This study demonstrated that CDU is a useful staging tool in breast cancer patients and may aid selection of patients for more appropriate axillary surgery and influence surgical management.

Poster 016

The effect of hormone replacement therapy on screen-detected breast cancers

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Background: Hormone replacement therapy (HRT) has been shown to increase the risk of developing breast cancer but cancers developing on HRT are said to have a lower grade and better prognosis. The aims of this study were to determine the effect of HRT on the prognostic factors of cancers detected at the incident screening round and compare these to tumours detected at the prevalent round.
Method: Tumour grade and size, lymph node status, presence of carcinoma *in situ* and history of HRT use were collected from patients with screen-detected cancers, 253 incident and 325 prevalent.
Results: HRT use was similar in prevalent (28·2 per cent) and incidence (28·9 per cent) groups.

	Grade 1		Grade 2		Grade 3	
	HRT	No HRT	HRT	No HRT	HRT	No HRT
Prevalent	30(40·5%)	51(20·0%)	34(45·9%)	166(65·6%)	10(13·5%)	36(14·2%)
All incidents	23(32·5%)	35(19·4%)	45(57·5%)	98(54·4%)	7(9·6%)	40(22·2%)
In situ cancer	11(47·8%)	13(37·1%)	22(52·3%)	33(33·7%)	1(14·3%)	16(40%)

Women who took HRT had more grade 1 tumours ($P=0·001$) detected at the prevalent round. This difference was reduced by the incident round ($P=0·1$) but these women developed fewer grade 3 tumours ($P=0·02$). Women who developed grade 3 tumours in the incident screen were found to have taken HRT for less time (mean 36·5 months [range 8–60]) than those with grade 2 (97·1 months [3–189]) or grade 1 tumours (150·5 months [8–158]). Carcinoma *in situ* occurred in more women taking HRT than those not (36/73 vs 63/180 $P=0·05$). No significant difference in nodal status was found.
Conclusion: Women taking HRT are less likely to develop high-grade tumours and more likely to develop an *in situ* lesion.

Endocrine

Poster 017

Parathyroidectomy for renal hyperparathyroidism: the transplant surgeon's perspective

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Background: Up to 10 per cent of patients receiving renal replacement therapy will require parathyroidectomy for secondary hyperparathyroidism. The aim of the current study was to report the management of this condition by a regional transplant unit.
Method: Between November 1994 and September 1997, 34 patients underwent parathyroidectomy for secondary hyperparathyroidism. The study population consisted of 20 male and 14 female patients of median age 41 (range 10–63) years. Renal replacement therapy was as follows: transplant ($n=17$), haemodialysis ($n=10$) and peritoneal dialysis ($n=5$). Two patients were pre-dialysis. Twenty-seven patients underwent subtotal parathyroidectomy and seven patients had a total parathyroidectomy with re-implantation.
Results:

	Preoperative median (IQR)	Postoperative median (IQR)	Statistical significance
Calcium (mmol/l)	3·03 (2·86–3·25)	2·39 (2·19–2·52)	$P<0·05$
Parathormone (pmol/l)	133 (99–150)	3·4 (0·9–11·1)	$P<0·05$
Alkaline phosphatase (IU/ml)	181 (121–237)	103 (63–152)	$P<0·05$
Symptoms: bone pain (%)	17 (50%)	2 (6%)	$P<0·05$
pruritus (%)	9 (26%)	2 (6%)	$P<0·05$

At a median follow-up time of 12 (range 1–33) months all patients are normolcacaemic. All patients with functioning grafts have normal parathyroid hormone (PTH) levels, however, six on haemodialysis have mildly elevated PTH (0 per cent versus 35 per cent, $P<0·05$).
Conclusion: Parathyroidectomy is effective in correcting the calcium biochemistry dysfunction seen in patients with chronic renal failure. Patients with renal transplants have a superior outcome compared to those on dialysis.

General

Poster 018

Impaired wound healing in patients with HIV infection and AIDS determined by biomechanical strength

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Background: Patients with HIV infection and AIDS with low CD4 counts, have been found to have impaired wound healing following both anorectal surgery and laparotomy. This study aims to determine whether the healed wounds from HIV and AIDS patients have an impaired intrinsic strength compared to non-HIV patients.
Method: The healed scars of patients with HIV and AIDS who were undergoing a subsequent surgical procedure were excised. The scars were examined immediately by tensionometry and the load extension curve used to calculate values of ultimate strength, resilience (energy absorbed to elastic limit), toughness (total energy absorbed before rupture) and extension to breaking point. A non-HIV group with scars in the same range of maturity as the HIV group also undergoing revision surgery were used as controls and the results compared using the Mann–Whitney U-test.
Results: The wounds of 11 patients with HIV and AIDS were compared to 11 controls. Wounds in both groups were between 4 months and 4 years in maturity with no significant difference of maturity between the two groups ($P=0·158$). The median age of the HIV group was 39 (range 29–60) years and that of the control group was 66 (range 28–83) years. There was no significant difference between the groups preoperative haemoglobin or albumin, however the white cell count was lower in the HIV group ($P=0·005$). When examined biomechanically, wounds from the HIV and AIDS group had a lower resilience ($P=0·0138$), toughness ($P=0·0138$) and maximum extension ($P=0·0235$) compared to those of the control group.
Conclusion: The wounds of patients with HIV and AIDS when measured biomechanically are weaker than those of non-HIV controls. This weakness of wound repair reflects an impairment of the healing process in these patients, and supports the clinical data which show poor wound healing following laparotomy and anorectal surgery.

Poster 019

Acute appendicitis and menstruation

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Background: This study aimed to determine the association of menstruation with acute appendicitis.
Method: Prospectively collected data utilizing computer-assisted diagnosis of acute abdominal pain used to review patients with histologically proven acute appendicitis.
Results: One thousand and forty-one consecutive patients with histologically confirmed acute appendicitis were studied between 1981 and 1990. Only 366 patients were female, of whom 314 were having menstrual cycles. Twenty-four patients were excluded (eight patients were pregnant, seven patients had missed a period without confirmed pregnancy and nine patients had no record in the notes of their menstrual cycle). The median age of the 290 patients studied was 21·2 years, range 9·7–50·5 years. Patients were subdivided into two groups according to their use of the oral contraceptive pill. In the group of 208 patients who were not taking the contraceptive pill, 82 had acute appendicitis while they were in the proliferative phase of their cycle, 109 in the luteal phase and 17 (8·1 per cent) while menstruating, which was significantly less ($P<0{\cdot}05$) than expected, based on a standard 28 day cycle. Eighty-two patients were on the contraceptive pill, five of whom had acute appendicitis while they were having a 'period' ($P=0{\cdot}074$). Clinical presentation (symptoms, clinical signs, white cell count) were not statistically different in menstruating patients compared with those in the proliferative or the luteal phase of the cycle or on the oral contraceptive pill. There was no increase of gangrenous or perforated appendicitis in the menstruating group.
Conclusion: Appendicitis is less frequent in women during physiological menstruation.

Poster 020

The role of intra-aortic balloon counterpulsation in emergency general surgery: case presentation and review of literature

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Background: Three cases are presented where intra-aortic balloon pump (IABP) was used prior to emergency non-cardiac surgery to stabilize the patient's cardiovascular status. The literature is reviewed for indications and clinical implications of counterpulsation and, in particular, the current concept of its use in emergency non-cardiac surgical procedures.
Method: Three patients who had recent myocardial infarction and required emergency life-saving procedure were included in this study. The IABP was inserted into the femoral artery by a Seldinger technique and placed in aorta. It was synchronized with the patient's pulse in a 1:1 ratio. The patients were monitored in the intensive care unit in the postoperative period.
Results: IABP successfully maintained the patients' cardiovascular status in the perioperative period.
Conclusion: IABP is a safe mechanical circulatory assistance device that improves cardiac function and reduces the risk of perioperative cardiac morbidity and mortality, although the experience is limited.

Poster 021

The driving force in trochar insertion

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Background: Insertion of the first trochar during the 'closed method' of creating pneumoperitoneum remains one of the most hazardous manoeuvres in laparoscopic surgery, with complications such as major vascular and bowel injuries. The ease with which trochars are inserted through the abdominal wall may well have some bearing on these complications.
Method: A range of both disposable and reusable trochars was investigated in experiments utilizing a hand-held pressure transducer and an abdominal wall model reconstructed with animal hide. Multiple insertions were performed and mean force of insertion recorded. A comparison of trochars was made and results listed in the following table.
Results:

Trochar type	Mean pressure (lb/in^2)
Best disposable	2·76 (0·12)
Best reusable	3·42 (0·03)
ANOVA	$P>0{\cdot}05$
New reusable	3·42 (0·03)
Used reusable	4·80 (0·05)
ANOVA	$P<0{\cdot}001$

Values in parentheses are SEM.

Conclusion: The effect of previous use on trochar performance demonstrates an obvious disadvantage of reusable instruments. The excessive force required to insert some trochars may place the patient more at risk of trochar injury.

Poster 022

Robotic assistant for laparoscopic cholecystectomy (Endosista): a clinical trial

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Background: Laparoscopic cholecystectomy usually requires an assistant to hold the telescope and camera, but camera control by the assistant is of varying quality, often unsatisfactory or unavailable. The aim of this study was to assess a robotic camera-holding device (Endosista) controlled by the surgeon's head movements in a clinical trial, and to compare it with a human camera holder.
Method: Patients undergoing laparoscopic cholecystectomy were randomized to have either the robotic or human assistant, with conversions to open operation excluded. Operating time, technical problems, the surgeon's and scrub nurse's subjective assessment, and complications were recorded. Consultants and trainees participated in the trial.
Results: Forty-two patients were randomized to Endosista (22) or manual assisted operations (20). Mean operating time with Endosista was 74 min (SEM 4 min) and 71 min with manual (SEM 5 min). There was no significant difference in operating times on an analysis of variance at the 95 per cent level. Use of the Endosista was readily learned, with no significant effect of occasion on operating time. Direct head control of the Endosista and the steady image provided were of significant benefit. The device was safe in use.
Conclusion: Endosista is a significant development for laparoscopic cholecystectomy, and is a safe alternative to a human assistant, providing a steady and high-quality image. Its use is easily learned by consultants and trainees.

Poster 023

The implications of a large population of intravenous drug abusers on surgical practice

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Background: The aim of this retrospective study was to assess the surgical complications associated with intravenous drug abuse and the resource allocation specifically associated with their treatment.

Method: All emergency surgical admissions to UCL Hospitals with complications of intravenous drug abuse over a 19-month period were audited (April 1996 to September 1997). Periods of in-patient care, surgical interventions, vascular complications, drug and total cost were calculated.
Results: Ninety-four intravenous drug abusers (31 women, 63 men of age range 18–49 years) were admitted. The majority of admissions were for localized sepsis associated with injection sites ($n = 90$) and four patients developed major vascular complications. Eighty-five per cent of patients required surgical intervention ($n = 80$). Of the total, 9 per cent ($n = 8$) were known to be either HIV or hepatitis B/C positive. The mean length of stay was 4·9 days (SD 5·93). The total cost of treatment was £130,000 and the mean cost per patient was £1382.
Conclusion: Although most patients had localized sepsis, a minority developed vascular complications necessitating more complex intervention with its associated financial implications. There is significant workload and resource implication for surgical units providing care to inner city drug abusers

Poster 024

Chronic abdominal pain and adhesions: patient assessment and surgical management with adhesiolysis and insertion of a bioresorbable membrane

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Background: The aim of this study was to assess our experience with patients whose intra-abdominal adhesions were thought to be causing symptoms and, in particular, the possible role of a new bioresorbable adhesion-prevention barrier (Seprafilm™).
Method: A review of patients referred with chronic abdominal pain attributed to intra-abdominal adhesions.
Results: Forty-one patients were referred between January and October 1997 for consideration of treatment for abdominal adhesions. There were 37 women and four men, and the median age was 45 (range 23–77 years). The median duration of symptoms was 6 (range 1–26 years). Two patients presented with purely obstructive symptoms, the remainder had chronic, disabling abdominal pain. All patients had undergone previous operations (laparoscopies: median 1, range 0–6; laparotomies: median 2, range 0–7). All patients had been extensively investigated elsewhere prior to referral. Fifteen of the 41 patients underwent an initial visceral slide ultrasound scan to look for the presence of adhesions to the undersurface of the abdominal wound. Of these 15 scans, six suggested adhesions to the back of the abdominal wound and in five no adhesions were present. In four the result was uncertain. The uncertain results were in wounds in the suprapubic region where the effects of exaggerated respiration are minimal. Six patients had a barium meal and follow-through, this showed no evidence of adhesions or obstruction in five but in one patient there was a suggestion of small bowel tethering which was confirmed at operation. Three patients underwent a barium enema examination which in one patient showed mild diverticular disease. Fifteen of the 41 patients went on to have a laparotomy with division of all adhesions and insertion of a bioresorbable membrane in an attempt to reduce adhesion reformation. Eleven of these patients have been seen postoperatively at 6 weeks or later. Ten of these patients report an improvement in their symptoms. Nine patients had a visceral slide ultrasound scan at a mean of 6 weeks postoperatively. Eight out of the nine scans were negative for adhesions. The one patient with a positive adhesion scan postlaparotomy was also the only patient to report a worsening of his symptoms.
Conclusion: Chronic abdominal pain attributed to adhesions is often complex and requires careful assessment and investigation before consideration of further adhesiolysis. A bioresorbable membrane has the potential to reduce adhesion reformation and offer symptomatic improvement, at least in the short term.

Poster 025

Central venous catheter-related sepsis: the inside story

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Background: Central venous catheter (CVC) tip roll has traditionally been used as the gold standard for diagnosing catheter-related sepsis (CRS) and has been the basis for the designs of new antimicrobial CVCs. This study was designed to look at the endoluminal and extraluminal segments of CVCs and to assess their significance in the development of CRS.
Method: Two hundred and thirty patients with suspected CRS were assessed over a 2-year period. The extraluminal colonization of CVCs was assessed using the tip roll technique, and endoluminal colonization using brush and tip flush techniques. CVC hub, skin and peripheral blood cultures were also performed. Scanning electron microscopy (SEM) was performed on proven cases of CRS (CRS defined as a positive catheter culture and associated peripheral bacteraemia with the same organism) to assess bacterial biofilms on both extra and endoluminal surfaces.
Results: Fifty-five cases of CRS were diagnosed (coagulase negative staphylococcus 20, *staphylococcus aureus* 14, candida 11, enterococcus 7, Gram-negative bacilli 3). Extraluminal, endoluminal and hub cultures were positive in 91 per cent, 100 per cent and 75 per cent of cases, respectively. More than 1000 colony-forming units were isolated from 45 per cent of extraluminal and 91 per cent of endoluminal samples. SEM performed on 12 cases of CRS showed significant endoluminally colonized biofilm, from hub to tip. SEM was unable to demonstrate extraluminal bacterial colonization in any of the CVCs assessed.
Conclusion: Endoluminal CVC colonization is highly significant in the pathogenesis of CRS, can be sampled *in situ* and should therefore replace extraluminal sampling in the diagnosis of CRS. Failure to coat the endoluminal surfaces of antimicrobial CVCs may explain why the use of these expensive catheters has failed to reduce CRS rates significantly.

Poster 026

What time of day should a urinary catheter be removed?

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Background: Urinary catheters are common on surgical wards yet there is little evidence upon which to base policy regarding the timing of their removal. This study was designed to determine whether urinary catheters should be removed in the morning or evening.
Method: All patients under the care of two consultants on a single general surgical ward with a short-term indwelling urinary catheter were prospectively randomized to removal either between 0700 and 0900 hours (early group) or between 2100 and 2300 hours (late group). End points included time to first void, volume of first void, frequency within the first 24 h, disturbance of normal sleeping hours and urinary retention.
Results: Of 123 patients, 66 were randomized to early removal and 57 to late removal. These groups were similar with respect to age, type of surgery and type of catheter. There was no significant difference between the groups of time to first void (mean 271 versus 327 min) but those undergoing early removal had a smaller first void (mean 221 ml versus 313 ml, Mann–Whitney, $P = 0·012$). The majority of those in the late group had their first void before 0600, and therefore had a disturbed night's sleep. Frequency of micturition was similar in each group. Recatheterization for retention was required in three patients in the early group (at 1500, 2330 and 0620 hours) and one in the late group (at 1200 hours) ($P > 0·2$).
Conclusion: There appears to be no particular medical advantage to catheter removal in the morning or evening. Late removal is associated with disturbance of sleep for micturition and early morning removal is preferable

Poster 027

The 'guarding probe': a laboratory assessment of a new device to measure abdominal rigidity in surgical patients

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Background: Abdominal rigidity, or 'guarding', is a fundamental but subjective surgical sign that influences many clinical decisions. The aim of this project was to develop a device capable of objectively measuring guarding.
Method: We developed a portable 'guarding probe' which simulates the action of the surgeon's hand when examining an abdomen. The device is pressed on to the patient's abdomen; displacement of a central probe is continuously correlated with the pressure generated at its tip. Data are automatically transferred to a laptop computer and plotted on a graph, the gradient of which gives a numerical value for guarding. We have assessed the guarding probe on a laboratory model and a small group of patients admitted with abdominal pain.
Results: a) In the laboratory model we used an inflatable model to simulate four different tensions in a mock 'abnormal wall' assessed by an experienced surgeon to be between 'normal' and 'rigid'.

Inflation pressure	Mean score	Range	Variance
5 mmHg	1·20	0·97–1·35	0·018
10 mmHg	1·61	1·53–1·74	0·005
15 mmHg	2·23	2·03–2·37	0·011
20 mmHg	2·81	2·74–2·99	0·007

b) In six patients the guarding probe was able to distinguish the three with peritonitis (score >1·20) from the three without peritonitis (score <1·00).
Conclusion: The guarding probe is a new device that can provide an objective score for abdominal rigidity or 'guarding', with excellent reproducibility in a laboratory model. Early clinical evidence suggests that this might be reproduced in the clinical setting.

Poster 028

Comparisons between NHS and private hospitals in the surgical management of inguinal hernia

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Background: This study aimed to compare current practice between the NHS and independent sectors in the surgical management of inguinal hernia in the UK.
Method: All surgeons and hospitals in two regions (South Thames and Northern and Yorkshire) performing groin hernia repair were identified and invited to participate. Participating surgeons completed a questionnaire for all patients over 18 years undergoing elective and emergency inguinal hernia repair between July and October 1996.
Results: Three hundred and eighty-five surgeons in 131 hospitals were identified. One hundred and eighteen hospitals participated. Two hundred and seventy-six of 368 (75 per cent) surgeons in these hospitals agreed to participate. Questionnaires from 5038 of 5556 patients were returned (90·7 per cent). Inguinal hernia repair was required in 4759 (94·5 per cent). Of these, 705 (15·1 per cent) were performed privately. Significantly more private operations (20·6 versus 10·1 per cent) were performed in South Thames. Fewer private operations (26 versus 42·5 per cent) were performed as planned day cases ($P<0{\cdot}0001$ χ^2). There was no significant difference in the rates of use of antibiotics. Fewer private cases were performed on an urgent or emergency basis (0·6 versus 2·8 per cent $P<0{\cdot}005$ χ^2) and fewer (3·0 versus 8·4 per cent) were in ASA class 3, 4 or 5 ($P<0{\cdot}0001$ χ^2). More private cases were performed using local anaesthesia (8·2 versus 5·4 per cent $P<0{\cdot}001$ χ^2).
Conclusion: Patients having inguinal hernia repairs performed privately were more likely to have them repaired laparoscopically. This may be because the costs of disposable equipment are too high for routine NHS use. More private operations were also performed using an open onlay mesh repair. More cases were performed using local anaesthesia but the rate was still very low. Fewer private operations were performed as planned day cases despite the pressures of private insurers. Private patients had a lower ASA score and were less likely to be performed on an urgent or emergency basis, suggesting differing case mixes. Significantly more private operations were performed in South Thames reflecting demographic differences.

Poster 029

Audit of 1125 surgical deaths from colorectal cancer in Scotland 1994–1996

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Background and Method: The Scottish Audit of Surgical Mortality (SASM), which examines all deaths on surgical wards in Scotland, collected data on the 1125 patients with colorectal cancer (799 colonic, 326 rectal) who died on surgical wards in 1994–1996.
Results: Sixty-five per cent of patients were >70 years, mean age 74 years (range 20–96), 64 per cent were admitted as an emergency; 54 per cent of operations were urgent/scheduled urgent, 61 per cent performed by consultants. The cause of death was cancer in 45 per cent and cardiopulmonary disease in 28 per cent; 363 patients received terminal care alone. A post-mortem was performed in only 16 per cent of patients but added information in just 2·5 per cent. Surgical assessors identified adverse factors in the choice of operation (3·1 per cent), preoperative management (7·2 per cent), intraoperative management (5·6 per cent), where technical operative problems were encountered in 17 per cent of patients, and postoperative management (11·8 per cent). Anaesthetic assessors identified adverse factors in the use of ITU/HDU (23·3 per cent) and in postoperative management (12·2 per cent). Over the 3-year period 1994–1996, adverse surgical factors declined as a contributor to death (from 20·3 per cent to 15 per cent) or cause of death (from 3·8 per cent to 0·8 per cent); anaesthetic factors remained static as a contributor or cause of death at 11·6 per cent and 0·6 per cent, respectively.
Conclusion: The SASM Audit has been associated with a fall in adverse surgical factors contributing to or causing death in patients with colorectal cancer. There remains room for increased consultant presence in theatre and improvement in postoperative management.

Poster 030

An audit of clinicopathological staging of cancers in the upper gastrointestinal tract in the South and West health regions

D.H. Bennett for the Upper GI Expert Tumour Panel of the South and West Regional Cancer Organisation *South and West Regional Cancer Organisation, c/o Professor A.N. Kingsnorth, Department of Surgery, Derriford Hospital, Plymouth*

Background: The advent of Cancer Centres nationwide has resulted in the need to audit the standard of treatment each centre is offering, leading to the development of a Regional Cancer Organisation (RCO). The role of the RCO is to both develop the minimum standards of care acceptable and to monitor, through audit, the performance of care against these standards.
Method: Three tumours were chosen for evaluation, oesophageal, gastric and pancreatic. A questionnaire was sent to each of the 27 hospitals covered by the RCO, requesting a pathology report and surgeon's operation note for one case of the above three tumours (a total of 81 tumours). The pathology report and surgeon's operative note were assessed by four independent clinicians using a standard proforma (13 and 12 questions,

respectively) for each tumour and, where there was disagreement, the result was adjudicated by a single member of the Expert Tumour Panel.
Results: There was no response from two hospitals despite repeated requests and, in some cases, the hospitals were not performing surgery for all three malignancies. This left 65 tumours (80 per cent) for analysis. Only 47 operation notes (58 per cent) were received and, of these, one was benign, two were frozen sections and one was the wrong operation note for the pathology report received. Therefore only 43 tumours (53 per cent) could be analysed, 10 pancreatic, 17 oesophageal and 16 gastric. Of these 43 tumours, none of the pancreatic and oesophageal tumours and only one of the gastric tumours could be accurately staged from the information received. The commonest reason for failure to stage the tumours (49 per cent of cases) was insufficient information on the radial resection margins. The presence of locoregional spread was also poorly documented (58 per cent cases only) and the extent of the resection (72 per cent cases only).
Conclusion: This study clearly indicates the urgent requirement for the standardization of both operations notes and pathology reports in order to provide sufficient information for oncologists to assess the need for additional treatment and for audit between centres.

Poster 031

Transthoracic endoscopic sympathectomy — no sweat!

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Background: There has been an increase in the use of transthoracic endoscopic sympathectomy (TECS) for the treatment of various conditions. The aim of this study was to review the results of a single centre.
Method: Between 1990 and 1996, 78 patients had 133 TECS procedures done; 70 patients were available for follow-up. Some 32 patients (23 female, mean age 26 years) were treated for hyperhidrosis of the axillae or hands.
Results: Seven (22 per cent) patients had residual pneumothorax; only one required chest drainage (3 per cent). One patient contracted Horner's syndrome (3 per cent) and six patients (19 per cent) had severe chest pain that delayed hospital discharge. At follow up (mean 3 years, range 6 months to 6 years), 93 per cent of patients who presented with palmar hyperhidrosis continued to have dry hands. Some 82 per cent of patients with axillary symptoms remained improved. Compensatory sweating occurred in 64 per cent of patients, gustatory sweating in 14 per cent and 36 per cent had continued neuralgia at the site-of-port insertion. Some 24 patients (18 female) of mean age 50 years had 38 limbs (14 bilateral, 10 unilateral) were treated for severe Raynaud's phenomenon of the hand. Early complications were similar to the hyperhidrosis group. TECS improved symptoms in all but three limbs (91 per cent). At follow-up (mean 29 months), 35 per cent of limbs continued to be better. Some 61 per cent of limbs had reverted to the preoperative state in a mean time of 17 months. TECS was done on 14 patients for angina, critical limb ischaemia or as an adjunct to upper-limb surgery.
Conclusion: These results show that TECS can produce excellent results for patients with hyperhidrosis of the hand and axilla. For those with Raynauds phenomenon the outcome is less good but sufficient to treat severe symptoms. Complication rates are low but the incidence of compensatory sweating is important. Most patients found the latter an acceptable price for dry hands.

Poster 032

Chronic groin pain following 'tension-free' hernioplasty

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Background: Chronic groin pain following inguinal hernia repair is a serious complication which may have a major effect on the patient's quality of life. The aim of this study was to examine the incidence of chronic groin pain following 'tension-free' hernioplasty.
Method: Between 1994 and 1996, 357 patients had mesh repair of a groin hernia under the care of one consultant. All have been examined for evidence of recurrence or chronic pain annually for 1–3 years.
Results: Results for chronic pain are as follows:

		Follow-up		
Year	No. patients	1 year	2 years	3 years
1994	113	16 (14%)	6 (5%)	7 (6%)
1995*	117	7 (6%)	4 (3%)	—
1996*	127	6 (4%)	—	—
Total	357	29 (8%)	10 (2·8%)	7 (1·9%)

*$P<0·05$ compared with 1994 group.

Twenty-four of the 29 (83 per cent) with chronic pain at 1 year complained of pain at the site of their hernia before operation compared with 62 per cent of the total number undergoing hernia repair. Chronic groin pain was more common after open than after laparoscopic repair 10 per cent versus 4 per cent ($P=0·02$). In six patients (1·7 per cent) the pain was of such severity that they required referral to the pain clinic.
Conclusion: The reduced incidence of chronic pain between operations performed in 1994 and 1995/96 suggests that this complication may be learning-curve related. As only two (0·6 per cent) have had evidence of recurrence, these data suggest that chronic pain after 'tension-free' hernioplasty is the most common long-term complication of this operation.

Poster 033

Value of preoperative and postoperative supplemental enteral nutrition in patients undergoing major gastrointestinal surgery

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Background: It has been proposed that supplemental enteral nutrition (SEN) administered to surgical patients in the postoperative period confers significant clinical benefit. We have investigated the potential advantages of SEN in 60 consecutive patients undergoing major excisional surgery.
Method: Patients were randomized to receive either normal diet or diet supplemented by commercially available nutrition 'sip feeds' (20 g protein, 600 kcal, 400 ml/day), for a minimum of 14 days prior to surgery and/or during the postoperative period. Pre- and postoperative weights, POSSUM scores, duration of hospital stay and any complications were recorded. Anthropometric measurements, serum proteins and liver function tests were serially measured. Patients were matched for age, sex and type of operation.
Results:

		Mean patient weights in kg (SEM)			
Group	Dietary supplement	Presentation	Pre-operative	Outpatient review	Duration of stay in days (SEM)
A ($n=15$)	Pre- + postoperative	62·1 (2·0)	61·8 (2·0)	61·2 (1·9)	11·8 (1·0)
B ($n=13$)	Pre-operative	64·0 (3·5)	61·1 (4·7)	54·0 (5·3)	12·8 (2·2)
C ($n=17$)	Postoperative	64·8 (3·1)	65·0 (3·1)	58·5 (3·4)	12·7 (1·4)
D ($n=15$)	None	69·8 (3·8)	71·5 (2·4)	68·5 (3·3)	13·4 (1·0)

All patient groups demonstrated a mean weight loss from time of randomization preoperatively to initial outpatient review following surgery (Table). Duration of hospital stay was the same in all groups. There were no inter-group differences in the incidence of complications, POSSUM scores, grip strength or biochemical indices.
Conclusion: Our results do not confirm the findings of others that short-term SEN confers significant clinical benefit.

Poster 034

The informed consent process in urgent abdominal surgery

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Background: We have previously reported to the Association that contrary to general medical opinion, patients with acute abdominal pain perceive that they retain the ability to give informed consent. However, as replies to questionnaires are critically influenced by the nature of the questions asked, this study aimed to evaluate the true significance of our previous findings by using a modified, non-leading questionnaire and by the use of two control groups.
Method: A prospective study of all patients over the age of 16 years admitted to an acute surgical unit and undergoing urgent abdominal surgery during an 8-week study period. Factors interfering with patients' ability to give informed consent were identified. Patients were asked if they had received an explanation of common side-effects and complications and if they knew the grade of the doctor obtaining consent. A control questionnaire was put to the consent obtainer to ascertain if there had been a discussion of potential side-effects and if an attempt had been made to avoid obtaining consent from patients under the effects of analgesia. A further control questionnaire was put to patients undergoing elective abdominal surgery to test the hypothesis that these patients are better informed. All questionnaires incorporated a mini-mental state test to allow recognition of those patients cognitively impaired at the time of interview. A consecutive series of 86 patients undergoing urgent surgery was evaluated of which 18 were excluded leaving a study population of 68. Seventy-seven patients undergoing elective surgery formed the control group.
Results: Forty-eight (71 per cent) patients undergoing urgent surgery reported that pain did not interfere with their ability to ask questions. Forty-six (68 per cent) patients had received analgesia prior to giving consent of which 14 (30 per cent) reported that this interfered with the ability to ask questions. Significantly fewer patients undergoing urgent surgery felt they had received an explanation of potential side-effects/complications of surgery compared to elective patients ($\chi^2=7{\cdot}3$, $P<0{\cdot}01$). Fourteen (21 per cent) patients undergoing urgent surgery correctly identified the grade of the doctor obtaining consent compared to 30 (39 per cent) undergoing elective surgery. Fifty-eight (85 per cent) patients undergoing urgent surgery felt that they retained the ability to give informed consent. Thirty-nine (57 per cent) doctors checked whether the patient had received analgesia prior to obtaining consent. Potential side-effects were discussed by 31 (46 per cent) and 10 (15 per cent) discussed alternative therapeutic options.
Conclusion: This study confirms that patients perceive that they retain the ability to give informed consent despite the effects of abdominal pain and analgesia. There is relatively little discussion of potential side-effects and complications in patients undergoing urgent surgery.

Poster 035

Peritoneal inflammatory cytokine response is increased following laparoscopy with cold carbon dioxide

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Background: Recent work has shown that intraoperative hypothermia is a significant source of surgical trauma with wide-ranging physiological and immunological sequelae. The aim of this study was to examine the effect of intraperitoneal hypothermia during laparoscopy on local inflammatory cytokine response in an animal model.
Method: Inbred Wistar rats ($n=28$) were randomized to undergo insufflation with CO_2 at room temperature (~21°C) or normothermic pneumoperitoneum. The latter consisted of CO_2 insufflated at 37°C with additional radiant and forced-air warming postoperatively to maintain normothermia. At 4 h and 24 h rats were sacrificed and peritoneal lavage performed to assess production of tumour necrosis factor (TNF-α). In addition, peritoneal macrophages were isolated and their activation was assessed *in vitro*, as shown by their TNF-α release following endotoxin challenge. Peritoneal fluid and macrophage supernatants were analysed by ELISA and data analysed by *t*-test.
Results:

	Cold CO_2	Warm CO_2	Significance
Lavage TNF-α (pg/ml) 4 h	17·01 ± 2·13	13·86 ± 1·08	$P=0{\cdot}09$
Lavage TNF-α (pg/ml) 24 h	18·05 ± 2·76	11·79 ± 2·69	$P<0{\cdot}02$
PMØ 4 h TNF-α (pg/ml)	362·1 ± 64·75	512·0 ± 83·22	$P<0{\cdot}02$

Laparoscopy with cold CO_2 results in a significant reduction in local and core temperatures ($P<0{\cdot}05$) and a significant inflammatory cytokine response with increased priming of peritoneal macrophages.
Conclusion: In agreement with previous work, this study shows that perioperative hypothermic stress in the form of cold gas insufflation is a significant source of surgical trauma which may be amenable to correction.

Poster 036

An objective assessment of surgeons' psychomotor skills: validation of the MIST-VR laparoscopic simulator

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Background: This study aimed to develop objective criteria for assessing psychomotor skill on a virtual reality simulator and to validate these measurements by comparing surgeons of differing experience.
Method: Thirty subjects [experienced laparoscopic surgeons > 100 cases ($n=10$), trainee surgeons ($n=10$) and non-surgeons ($n=10$)] were given identical training on a virtual reality simulator (MIST-VR) to familiarize them with the equipment. The subjects were then asked to perform ten repetitions of a complex virtual task which involved two-handed co-ordination and use of a foot pedal to simulate diathermy. The position in space of left and right virtual instrument tips was tracked and the x,y,z co-ordinates recorded every 0·05 s. Comparison of these data with the x,y,z positions of the virtual tasks enabled the computer to calculate efficiency of movement (actual/ideal path length), number of past-pointing errors, number of sub-movements needed to complete the task and total time taken.
Results:

	Efficiency (path length ratio)	Errors (past pointing)	Sub-movements	Time taken
Experienced	2·3 (0·3)	4·7 (1·1)	10·1 (3·4)	13·3 (3·2)
Trainees	3·3 (1·3)	6·3 (2·3)	15·9 (4·4)	19·3 (5·4)
Non-surgeons	3·6 (1·0)	7·3 (2·2)	18·5 (6·1)	21·9 (6·7)
Significance (Kruskal–Wallis)	$P<0{\cdot}01$	$P<0{\cdot}02$	$P<0{\cdot}01$	$P<0{\cdot}01$

Values are mean (SD).

Conclusion: A virtual reality simulator can distinguish between experienced surgeons, trainee surgeons and non-surgeons by unbiased objective measurement. The ability to quantify technical expertise could have implications for training, examination and accreditation.

Poster 037

Aterial natriuretic peptide expression and secretion in laparoscopic and open surgery

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Background: Abdominal insufflation required for laparoscopic surgery causes a significant reduction in femoral vein and inferior vena caval

(IVC) blood flow. We have recently shown that IVC pressure increases significantly on induction of pneumoperitoneum and is maintained until desufflation. Such venous pressure changes are not apparent during 'open' surgery. We considered the effect that these changes in venous pressure and flow have on the expression and secretion of atrial natriuretic peptide (ANP), an important regulator of cardiovascular function.
Method: Male Sprague–Dawley rats (weight 400–550 g) were randomized to control (anaesthetic alone), CO_2 pneumoperitoneum for 1 h (intra-abdominal pressure 8–10 mmHg) or laparotomy for 1 h. After the animals were killed, blood was taken by direct cardiac puncture for measurement of serum ANP (using an enzyme-linked immunosorbant assay) and atrial tissue removed for RNA extraction. Differential reverse transcription-polymerase chain reaction (with β-actin as the internal standard), was used to detect and semi-quantify the ANP mRNA present in 1 μg extracted RNA.
Results: The ANP mRNA data are shown below as a percentage of the control.

	ANP mRNA levels	[ANP] pg/ml
Control		93·5 (12·8)
Pneumoperitoneum	66·8 (7·5*)	57·4 (9·3)
Laparotomy	29·7 (1·0†)	37·9 (9·9‡)

Values are mean (SEM). For each experimental group n = 7 to 9. *P = 0·05 and †P = 0·001 versus control (t-test); ‡P = 0·05 versus control (Mann–Whitney U-test).

Conclusion: There is a significant reduction in the expression of ANP mRNA after 1 h pneumoperitoneum, with a similar trend in ANP release. While this fall corresponds to the observed fluctuation in IVC pressure and blood flow, such a mechanism does not explain the more pronounced reduction in ANP seen following laparotomy. We suggest an alternative mechanism controls ANP expression and release in open surgery, which is independent of venous pressure.

Poster 038

The use of carbon dioxide laser to control cutaneous limb recurrence from malignant melanoma

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Background: Surgical excision of cutaneous malignant melanoma metastases is only practical when the number of lesions is small. In lesions confined to the limbs, isolated limb perfusion (ILP) has been our treatment of choice for the past 10 years. This, however, is not possible in all patients. We present our experience with carbon dioxide laser ablation as an alternative treatment in the control of cutaneous metastases in such patients.
Method: Between September 1992 and November 1996, 29 patients (20 female and nine male) underwent a total of 57 laser treatments. The lesions were situated on the face, chest, arm and leg. The number of lesions per patient ranged from two to 43 nodules. A Sharplan 1030 portable carbon dioxide laser was used. All procedures were carried out under general anaesthesia. Each lesion was destroyed using a focused laser beam of 10–20 watts with a beam size of 0·5–1·0 mm.
Results: Twelve patients have had multiple laser treatment in the attempt to control local disease, the most being seven treatments in one patient. At a mean follow-up of 18 months, six patients have died from the disease. In the 23 patients who are alive, 18 have had no recurrence of the disease and five have had partial control of local disease.
Conclusion: Our experience suggests that carbon dioxide laser ablation of cutaneous metastases is a minimally invasive procedure which gives effective palliation.

Poster 039

The confidential enquiry into surgical training

The Advisory Committee on Audit (D.R. Harper) *Royal College of Surgeons of Edinburgh, Edinburgh*

Background: This study aimed to audit the contribution made to junior surgical training in the operating theatre by training consultants.
Method: Two hundred Scottish surgeons across all specialities collaborated in this study by agreeing that data from theatre computer systems could be directly accessed by the Royal College of Surgeons of Edinburgh. In the event these systems could only produce reliable data with respect to the work of a third of participating consultants. The data were standardized by examining certain representative operations only, the indicator operations, which varied from speciality to speciality. Each surgeon's data were returned to him compared with the pooled data of all the surgeons in the speciality.
Results: The data allowed analysis of five scenarios for 968 operations: trainee operating with the consultant surgeon assisting, consultant surgeon operating with the trainee assisting, a trainee operating with a trainee assisting, a trainee operating alone, and other scenarios.

There was considerable variation between and within specialities. For example, the average percentage of cholecystectomy cases where a trainee was taken through by a consultant was 21·5 per cent. However, the caseload of the surgeon bore no relationship to the proportion of times that his trainee had the opportunity of hands on experience, although by comparison with the previous year many surgeons improved their practice.
Conclusion: Surgeons are open to the idea that their contribution to training at the operating table is sufficiently important to allow their data to be used in this way. There is evidence that this audit changes practice for the better. Hospitals having trainees should have systems to allow this kind of audit to take place.

Hepatobiliary/Pancreatic

Poster 040

Scottish audit of surgical mortality from pancreatic cancer 1994–1996

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Background: The Scottish Audit of Surgical Mortality collects data on the management of patients who die in surgical wards. The aim of this study was to identify areas for improvement in the management of patients who die from pancreatic cancer.
Results: During the first 3 years of the audit (1994–1996), there were 334 deaths; 165 (75 per cent) were emergency admissions, 133 (40 per cent) had an operative procedure. In 147 (44 per cent) the patients' treatment was limited and 94 (28 per cent) had terminal care. Seventy (53 per cent) operations were performed as urgent or emergency, 18 (14 per cent) had an open and shut laparotomy, but only eight (2·1 per cent) deaths followed pancreatic resection. In 21 (16 per cent) patients there were intraoperative technical problems and 25 (19 per cent) patients required reoperation for complications. Adverse factors in surgical management were identified in 16 (12 per cent) patients and in anaesthetic management in six (5 per cent) patients. Postoperative care could have been improved in 23 (17 per cent) patients and 17 (13 per cent) who would have benefited from HDU/ITU care were denied it.
Conclusion: This study has identified areas for improvement in the management of patients with pancreatic cancer managed on surgical wards.

Poster 041

Thromboprophylaxis and the incidence of deep vein thrombosis and pulmonary embolism following laparoscopic surgery

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Background: Despite the increased risk of venothrombosis with laparoscopic surgery there is still great variation between surgeon's choice of thromboprophylaxis. We have reviewed the different thromboprophylaxis protocols and audited the venothrombotic rate following laparoscopic surgery at our hospital.

Method: A telephone survey of thromboprophylaxis regimen, used by surgical firms with an established laparoscopic practice in Wales, was conducted. In order to determine the effectiveness of these regimes an audit of venothrombotic complications at our hospital following laparoscopic procedures for the past 5 years was also conducted.
Results: There were 19 surgical firms in 14 centres. Four surgical firms (21·1 per cent) do not use routine prophylaxis. Of the remaining 15 (78·9 per cent) firms, 13 (86·7 per cent) use TEDS, 7 (53·9 per cent) use IPCS and 13 (86·7 per cent) use miniheparin routinely. Eleven firms (57·9 per cent) will alter their prophylactic regime with high-risk patients. None of the firms reported venothrombotic complications that they were aware of. Between 1991 and 1996 there were 2224 laparoscopic procedures performed at our hospital. Of these, 1202 procedures were performed by general surgeons with the majority being laparoscopic cholecystectomy. The rest were mainly gynaecological diagnostic procedures. There were no venothrombotic complications following laparoscopic procedures during this period.
Conclusion: There is great variability of choice of thromboprophylaxis between surgeons for laparoscopic surgery. Surprisingly, the clinical result does not appear to support the increased risk of venothrombosis following laparoscopic surgery.

Poster 042

Good outcome from surgery for ampullary tumour: a 16-year review

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Background: Ampullary tumours are rare with a few reported series but appear to have a better prognosis than pancreatic neoplasms. The aim was to review the management and long-term outcome of patients admitted to the Surgical Unit with an ampullary tumour from January 1980 to April 1997.
Method: Patient records were reviewed.
Results: Twenty-six cases of ampullary tumours were admitted, 21 adenocarcinoma, five benign tumours including two neuroendocrine tumours (carcinoid, gangliocytic paraganglioma) and three adenomas. All patients had endoscopic biopsy. The benign tumours were found in five men, aged 42–73 years (mean 58 years) and were treated by transduodenal local resection (4) and Whipple procedure (1). One in-hospital death at 2 months occurred from anastomotic leak in the Whipple procedure patient. Ten men and 11 women had adenocarcinoma, with a mean age of 74 years (range 43–91 years). Patients presented with jaundice (17), pain (9), weight loss (8), lethargy (4), recurrent pancreatitis (2), anaemia (2), liver metastasis (1). Two patients were asymptomatic with tumours found incidentally at cholecystectomy. One patient aged 89 years had palliation only. Two patients had biliary stenting only (one aged 91 years, the other aged 67 years who refused surgery). Three patients had preoperative stenting. Six patients had a Whipple procedure, seven had a pylorus-preserving pancreaticoduodenectomy (PPPD), two had local resections, two had palliative bypass surgery. There were no 30-day or in-hospital mortalities. The 5-year survival following PPPD was 43 per cent and Whipple 33 per cent. Both local resection patients died within 5 years, but not from recurrent disease.
Conclusion: Our experience suggests that benign ampullary tumours may be safely resected locally and that pancreaticoduodenectomy for adenocarcinoma of the ampulla has a favourable operative and long-term mortality.

Poster 043

Audit of deaths from acute pancreatitis in the south east of Scotland 1995–96: evidence for variation in management?

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Background: This study aimed to undertake an audit of all deaths under surgical care from severe acute pancreatitis in the South East of Scotland, 1995–96.
Method: All patients with a diagnosis of acute pancreatitis reported to the Scottish Audit of Surgical Mortality (Edinburgh Office) during 1995–96 were included. Age, sex, surgical intervention, mode of death, length of stay, deep venous thrombosis prophylaxis and intensive care unit admission were noted.
Results: Sixty-one deaths were reported. The median age was 70 (range 31–91) years with 13 patients (21 per cent) under the age of 55 years. Thirty-six patients were male, seventeen patients underwent surgical intervention, necrosectomies (13), drainage of pseudocyst (2), ERCP (2). Diagnosis of severe acute pancreatitis was made at presentation in 56 patients (92 per cent), at post-mortem in four and at laparotomy in one. The predominant mode of death was multiple organ failure (49 patients). Of the remainder, three died from pancreatitis complicating terminal cancer, three from myocardial infarction, three from pulmonary embolus (one in the presence of multiple organ failure), two from peripancreatic haemorrhage, one from a bleeding duodenal ulcer and one from a stroke. The median time from admission to death was 8 days (4·5 days in those >55 years versus 16, <55). Twenty patients (33 per cent) died within the first 48 h. Thirty-five patients were managed in specialist units, 14 of whom had been transferred from other units. In three patients, delay in transfer was thought to contribute to their death. Ten out of 26 patients (surviving >48 h) were not transferred to specialist units despite their diagnosis being known and there being no decision to limit treatment. While pulmonary embolus contributed to death in three patients, deep vein thrombosis (DVT) prophylaxis was not used in 29 patients (48 per cent); seven of whom had deranged coagulation but no reason was given in 22 patients. Forty patients (66 per cent) were admitted to the intensive care unit (ICU). There were no ICU beds available for three patients and a decision to limit treatment was made for eight patients. No reason was given for the remaining 10 patients whose ages ranged from 75 to 89 years.
Conclusion: A third of patients dying from acute pancreatitis rapidly develop MOF and die within 48 h of admission. Some patients were either not transferred to specialist units or were transferred late; DVT prophylaxis was not universal; ICU facilities were withheld from a number of elderly patients, but the reasons for such variation in surgical management cannot be eludicated from this audit.

Poster 044

Prospective randomized trial of mini-cholecystectomy versus laparoscopic cholecystectomy: a single surgeon study

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Background: This study aimed to prospectively examine laparoscopic and mini-cholecystectomy and discover if they are comparable operations for the treatment of patients requiring elective cholecystectomy.
Method: Patients awaiting elective cholecystectomy without clinical suggestion of bile-duct stones were randomized to either laparoscopic or mini-cholecystectomy. Procedures were all performed by one surgeon (FPMcG) with experience (60 cases) of both forms of surgery.
Results: Operative duration was shorter and postoperative stay longer for mini-cholecystectomy (53 versus 69 min, $P<0{\cdot}01$, 3·5 days versus 3 days (mean) $P<0{\cdot}05$; Mann–Whitney U-test). Major complications were more common after laparoscopic cholecystectomy (5 versus 1, $P<0{\cdot}05$; Fishers exact test).
Conclusion: This study suggests that postoperative complications after laparoscopic cholecystectomy may be more common than after mini-cholecystectomy. A large, multi-surgeon, prospective study is required to establish the safety of laparoscopic cholecystectomy compared with mini-cholecystectomy.

Poster 045

Management of hepatobiliary Ascaris infestation after failed medical treatment

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Background: *Ascaris lumbricoides* is endemic in much of Africa. Around 20 per cent of all ascariasis-related admissions are for hepatobiliary

disease and the majority of these patients will respond to standard medical therapy (cessation of oral intake, i.v. fluids, antispasmodics, and anti-helminthic drugs). When medical therapy fails, surgery has been the traditional treatment of choice. The aim of this study was to determine the role of endoscopic retrograde cholangiopancreatography (ERCP) and surgery in the management of hepatobiliary Ascaris.
Method: Analysis of all patients undergoing ERCP or surgery for ascariasis of the biliary or pancreatic system unresponsive to standard medical therapy. Worms were extracted using snare or biopsy forceps. Success was defined as clearance of worms and eradication of symptoms.
Results: ERCP extraction was attempted in 25 patients with success in 19 (76 per cent). The median number of procedures was 1 (range 1–5). Concomitant calculi were present in six patients. Two patients suffered complications: 1 empyema, 1 pseudocyst. Failed clearance of worms by ERCP was due to gallbladder-related disease in two patients, strictures in three and intrahepatic worms in one patient. All six patients were successfully treated by surgery [laparoscopic cholecystectomy (1), open cholecystectomy (1), exploration of CBD (1), roux-en-Y hepaticojejunostomy (2) and longitudinal pancreaticojejunostomy (1)].
Conclusion: ERCP is successful in the treatment of Ascaris infestation resistant to medical therapy in 76 per cent of patients. Surgery remains important in the management of Ascaris infestation associated with the gallbladder, and with biliary or pancreatic strictures.

Poster 046

Magnetic resonance-guided interstitial laser thermoablation in an isolated perfused organ model

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Background: Magnetic resonance imaging (MRI) is the most sensitive radiological modality for on-line monitoring of interstitial laser thermoablation (ILT). We developed an isolated perfused organ model to evaluate the relationship between energy deposition and lesion size in the presence of the heat-sink effect from simulated blood flow.
Method: In fresh porcine livers an MR-compatible perfusion cannula was placed within the portal vein. The livers were positioned within a laparoscopic simulator in a 0·5T MR scanner and connected via 15 m of silastic tubing to a single-chamber cardiac perfusion pump with heat-exchanger (positioned outside the magnet room). Perfusate return was via sump drainage from the simulator. The livers were perfused at 500 ml/min with University of Wisconsin solution at 4°C. A freshly cleaved 600 μm diameter bare Nd:YAG laser fibre was placed within the parenchyma together with an MR compatible thermocouple. Real-time MR monitoring was performed with a novel colour subtraction sequence during lesion formation at 5 W for 20 min or 10 W for 10 min (total energy deposition 6000J). The temperature at the tip of the laser fibre was measured at minute intervals. The maximum dimensions of the resulting lesions were measured at histology and compared with those predicted from the on-line MR imaging.
Results: Porcine livers could be perfused using this model at 4°C for 8 h with maintenance of tissue viability as assessed by histological methods. The spatial and temporal extent of lesion formation was monitored successfully using the colour subtraction sequence in each case. There was a significant difference ($P<0{\cdot}01$) between maximum temperature (mean ± SD) reached at 5 W (34·3 ± 18°C, range 13–63°C) and at 10 W (84·2 ± 31·5°C, range 25–153°C). Maximum lesion size (mean ± SD) at 5 W was 1·3 ± 0·4 cm (range 0·8–1·6 cm) and 2·0 ± 0·3 cm (range 1·5–2·5 cm) at 10 W. The difference between mean lesion size at 5 W and 10 W was significant ($P<0{\cdot}01$). Lesion size measured at histological examination correlated closely with that predicted from the image ($r^2=0{\cdot}84$). The smaller lesions occurred when the fibre was placed in close proximity to a large intrahepatic branch of the portal vein.
Conclusion: This perfused organ system allows the effect of simulated blood-flow on MR-monitored ILT to be studied *in vitro* and could potentially be applied to the study of ILT in perfused human tissues at normal body temperature. The maximum temperature reached during formation of an ILT lesion, and hence maximum lesion size, depends on both the laser power settings and the proximity of the fibre to large blood vessels.

Poster 047

Increased nitric oxide activity in acute pancreatitis

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Background: Over-production of nitric oxide (NO) via induction of the inducible NO synthase (iNOS) is increasingly recognized as an important factor in the haemodynamic disturbances of several inflammatory states. The aim of this study was to identify the role of NO in a caerulein-induced model of acute pancreatitis in the rat.
Method: Acute oedematous pancreatitis was induced by caerulein in 10 adult male Wistar rats. Blood pressure and plasma NO metabolites were measured at 0 and 7 h, pancreatic iNOS activity was assayed biochemically by measuring conversion of radio-labelled L-arginine to L-citrulline. In addition, the pancreatic expression and cellular localization of iNOS and nitrotyrosine (a marker of peroxynitrite-induced oxidative tissue damage) were characterized by immunohistochemistry. Data were compared to those in saline-treated controls ($n=10$).
Results: Compared with controls at 7 h, the pancreatitis group displayed raised plasma NO metabolites [mean (SEM) 70·2 (5·9) versus 22·7 (2·2) μmol/l, $P<0{\cdot}0001$] and reduced mean arterial blood pressure [88·7 (4·6) versus 112·8 (4·1) mmHg, $P=0{\cdot}001$]. There was marked iNOS activity in the pancreatitis group [3·1 (0·34) versus 0·1 (0·01) pmol.mg protein^{-1}.min^{-1}, $P<0{\cdot}0001$]. There was also increased localization of iNOS within vascular smooth muscle cells ($P=0{\cdot}003$ versus controls), with positive perivascular staining for nitrotyrosine ($P=0{\cdot}0012$ versus controls).
Conclusion: In this experimental mode of acute pancreatitis, iNOS induction and oxidative tissue damage in the pancreas is associated with raised systemic NO and arterial hypotension. Excess production of NO arising from the inducible NO synthase may be an important factor in the systemic and local haemodynamic disturbances associated with acute pancreatitis.

Poster 048

Comparison of laparoscopic cholecystectomy in obese, morbidly obese and non-obese patients

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Background: This study aimed to evaluate the influence of morbid obesity on feasibility and outcome of laparoscopic cholecystectomy (LC).
Method: Data collected prospectively from 864 consecutive patients undergoing LC at our institution between 1990 and 1997 were analysed. This series represents a continuing policy of LC for all-comers. There were 659 non-obese (Group I: BMI <30 kg/m^2), 188 obese (Group II: BMI 30–40 kg/m^2) and 17 morbidly obese patients (Group III: BMI >40 kg/m^2). Groups were well matched for age and sex distribution.
Results: A trend towards increased conversion rate, operative time and postoperative complications, and reduced ability to obtain cholangiography was observed with increasing obesity. This, however, was not statistically significant (χ^2 test, $P>0{\cdot}05$). There were no operative deaths in either group. Postoperative hospital stay for LC was similar in all groups (median: 1 day).

	Group I	Group II	Group III
Conversions	15 (2·3%)	8 (4·3%)	1 (5·9%)
Mean operative time (min)	95	96	112
Postoperative complications	31 (4·7%)	11 (5·9%)	2 (11·8%)
Operative cholangiography*	491/570 (86%)	141/176 (80%)	10/14 (64%)
Bile duct exploration	28 (4·2%)	9 (4·8%)	1 (5·9%)

*103 (12 per cent) patients who had clear duct at preoperative ERCP, operated on by surgeons adopting selective cholangiography or underwent a planned laparoscopic duct exploration were excluded from this analysis.

Conclusion: LC in morbidly obese patients appears safe with no significant increase in operating time, postoperative complications, or hospitalization.

Poster 049

Bacterial colonization of the upper gastrointestinal tract is associated with septic morbidity in patients with acute pancreatitis

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Background: Pathological colonization of the normally sterile upper gastrointestinal tract may be an important prelude to the development of septic complications in critically ill patients. We have correlated the results of nasogastric aspirate culture and severity of illness with the incidence of septic complications in patients presenting with acute pancreatitis.
Method: Thirty-four patients with acute pancreatitis underwent nasogastric intubation as part of standard clinical treatment. Gastric aspirate (10 ml) was obtained under sterile conditions and sent for microbiological culture. Physiological assessment scores (POSSUM) were measured in all patients. All septic events were recorded.
Results: Patients with multi-organism colonization had a significantly greater incidence of septic complications compared to those with single or no organisms isolated from the aspirate (6 of 8 versus 2 of 8 positive; 8 of 26 versus 18 of 26 negative, $P<0{\cdot}05$). Furthermore, patients with a low POSSUM score (<20) had a significantly lower incidence of septic events and aspirate culture growth. Lactobacilli were frequently isolated in non-septic patients (20 of 26, mean POSSUM score 17 ± 2) but were absent in all but one of the patients with septic complications (1 of 8; mean POSSUM score 34 ± 4, $P<0{\cdot}05$).
Conclusion: Bacterial colonization of the upper gastrointestinal tract predisposes to septic complications in patients with acute pancreatitis.

Poster 050

Oral eicosapentaenoic acid reduces experimental human pancreatic tumour growth in SCID mice

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Background: We have previously shown that eicosapentaenoic acid (EPA) will inhibit the growth of human pancreatic cancer cell lines *in vitro*. This study aimed to assess the effect of dietary EPA upon the growth of a human pancreatic cancer cell line (MIAPaCa-2) as a xenograft in immunocompromised mice.
Method: Pieces of tumour were transplanted subcutaneously in the flank of 5–6 week old female SCID mice. From the day after implantation mice were fed a fat-free diet to which was added either 5 per cent (final diet weight) corn oil or 4 per cent EPA (as free acid) plus 1 per cent corn oil. Mice were killed before the tumour burden became excessive at around 3 weeks. Matched groups of animals without tumours were also studied.
Results: Mice fed the diet enriched with EPA had significantly smaller tumours than control animals [median 2810 mm^3 (interquartile range 2050–3790) versus 4960 mm^3 (range 3210–6320), $P=0{\cdot}023$]. Liver and spleens of tumour-bearing animals were substantially heavier than non-tumour-bearing controls ($P<0{\cdot}001$) due to metastases. Liver and spleens of tumour-bearing animals were significantly lighter in those fed EPA compared with those fed corn oil ($P<0{\cdot}001$) suggesting a reduced metastatic burden. As mice fed EPA ate significantly less food than controls (2·25 g/day versus 3·05 g/day, $P=0{\cdot}021$) and caloric intake will influence tumour growth in similar models, the experiment was repeated supplying matched amounts of food. Again tumours were smaller in EPA fed mice [3080 mm^3 (1800–3900) vs 4800 mm^3 (3060–6400), $P=0{\cdot}027$) and liver and spleens were lighter with EPA ($P<0{\cdot}02$) suggesting that tumour growth reduction was due to EPA and not diet restriction.
Conclusion: We conclude that 6–8 g/kg/day EPA within the diet will slow the growth of a human experimental tumour and reduce metastatic spread in a mouse model. The potential of EPA as a non-toxic anti-cancer agent deserves further study in human neoplastic disease.

Poster 051

Role of laparoscopy and laparoscopic ultrasonography in the surgical management of cholangiocarcinoma

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Background: This study aimed to evaluate the contribution of laparoscopy and laparoscopic ultrasonography in surgical decision making in the management of cholangiocarcinoma.
Method: Data on 35 patients who had laparoscopy and laparoscopic ultrasonography as part of their work up were collected retrospectively. The information provided by this investigation in addition to computed tomography (CT) scan and angiography was assessed.
Results: Of the 35 patients in the study, 22 had angiography and 31 had CT scans. Laparoscopy and laparoscopic ultrasonography predicted inoperability in 15 patients when CT and angiography had already suggested inoperability in seven of these. Of the remaining eight, five had peritoneal seedlings, two ascites and one had main portal vein involvement precluding curative surgery. Twenty-one patients (including one deemed irresectable on laparoscopic ultrasonography) underwent surgery. Curative resection could be achieved only in 13 patients (nine pancreatico duodenectomies, three hepatectomies and one bile duct resection). Laparotomy in the one patient, in whom laparoscopic ultrasonography suggested irresectability, confirmed irresectability and segment III cholangiojejunostomy was undertaken.
Conclusion: Laparoscopy contributes to the management of cholangiocarcinoma by excluding patients with peritoneal dissemination from unnecessary laparotomy. The additional information provided by laparoscopic ultrasonography does not add to the assessment of resectability — particularly local invasion for hilar cholangiocarcinomas where a Segment III cholangiojejunostomy provides the most effective surgical palliation.

Poster 052

Hepatic resection for colorectal cancer metastases

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Background: This study aimed to assess the results of hepatic resection for colorectal cancer metastases.
Method: From 1986 to 1997, 86 consecutive patients undergoing liver resection for colorectal metastases with curative intent were studied. Fifty-one of them had major resections and 28 had minor resections. In 20 patients the liver secondaries were detected synchronously with the primary tumour. The other 66 had the liver involvement detected at a median of 21·2 months after resection of the primary colonic neoplasm. The liver was affected by single lesions in 55 patients and by multiple lesions in 32. The median size of the lesions was 6·1 cm and the median follow-up period was 23·9 months.
Results: The actuarial 1, 3 and 5 years survival for these patients was 75·4 per cent, 42 per cent and 26 per cent, respectively. The perioperative mortality rate was 2·3 per cent. There were no significant differences in the overall survival concerning the diagnosis of synchronous or metachronous metastases, nor in the number or size of the hepatic lesions when analysed as isolated parameters.
Conclusion: Liver resections for colorectal cancer metastases are relatively safe procedures and can offer the potential for prolonged long-term survival.

Poster 053

Lipiodol enhanced computed tomography scanning of liver tumours

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Background: Lipiodol, an iodized poppy seed oil, is a contrast medium which has been shown to be taken up and retained selectively by primary and some metastastic liver cancers, following injection into the hepatic artery. This study aimed to assess the sensitivity of Lipiodol enhancement of computed tomography (CT) scanning of the liver in the diagnosis of liver tumours.
Method: Over a period of 6 years (1989–1995), all Lipiodol-enhancing CT scans of the liver were assessed retrospectively, and a grading classification was performed independently by a surgeon and a radiologist. Maki's grading of uptake of Lipiodol was carried out (grade IV = >90 per cent uptake, grade III = 50 per cent, grade II = 20–50 per cent, grade I = <10 per cent poor uptake). A total of 107 Lipiodol-enhanced CT scans were assessed. Hepatic angiography was carried out on all of these patients for diagnostic purposes, with intrahepatic arterial administration of 10 ml of Lipiodol emulsified in 10 ml of Urografin. A repeat Lipiodol CT scans of the liver were obtained 7–14 days after the intra-arterial injections of Lipiodol. A histological confirmation of the diagnosis was obtained for all the patients who were shown to have tumours on CT scanning.
Results: Forty-two patients were shown to have hepatocellular carcinoma, in whom Lipiodol-CT was diagnostic in 40. Nine patients had colorectal hepatic metastases (Lipiodol-CT was diagnostic in eight), and five patients were shown to have other metastatic tumours (Lipiodol-CT was diagnostic in all). Lipiodol-CT scans showed no uptake in normal or benign liver lesions, and was very helpful as a diagnostic tool. There was good correlation in the grading of Lipiodol uptake between the surgeon and the radiologist (98 per cent correlation). Patients with hepatocellular carcinoma showed a high degree of Lipiodol uptake, while the uptake and retention of Lipiodol in the patients with colorectal metastases was variable and inconsistent. Two liver transplant patients were shown to have early hepatomas.
Conclusion: Lipiodol-enhanced CT scanning is a valuable tool in detecting hepatocellular carcinoma and neuroendocrine tumours, with good uptake of Lipiodol (grade IV). The uptake in hepatic metasases of colorectal, renal and breast cancers is poor (grade II).

Coloproctology

Poster 054

[Anti-17.1A × anti-CD3] F(ab′)$_2$ bispecific antibody inhibits growth of pulmonary metasteses in mice bearing syngeneic 17.1A-transfected tumour

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Background: Monoclonal antibody 17.1A confers a survival advantage on patients with high-risk colonic carcinoma and we have recently demonstrated that the bispecific F(ab′)$_2$ antibody heteroconjugate anti-17.1A × anti-CD3] can target human cytotoxic T lymphocytes against human colonic carcinoma *in vitro*. In the present study, we have examined the ability of T cells retargeted with an equivalent bispecific antibody to inhibit the growth of tumour in a murine model of metastatic disease.
Method: C57/BL mice were injected intravenously with syngeneic 17.1A-transfected B16 melanoma cells. Therapy with 17.1A immunoglobulin (IgG), [17.1A × CD3] F(ab′)$_2$ bispecific antibody and controls, was given both i.v. and i.p. on day 1 and i.p. daily for 9 days thereafter. Animals were killed on day 21. Their lungs were removed and the number of surface metasteses counted.
Results: Treatment with the bispecific F(ab′)$_2$ antibody derivative proved to be more efficacious than therapy with 17.1A IgG and resulted in a marked and significant (more than two-fold) reduction in the mean number of pulmonary metastatic deposits in that group of animals (mean number of tumour metasteses 59 cf. 157; $P<0.05$). Moreover, there was a highly significant reduction in the mean number of metastic deposits in mice treated with the bispecific heteroconjugate compared with controls (59 cf. 435; $P<0.005$) and therapy with 17.1A IgG compared with controls (157 cf. 435; $P<0.02$). Neither the bivalent anti-17.1A Fab′$_2$ nor anti-CD3 Fab′$_2$ therapy resulted in any measurable reduction in tumour burden when compared with the other treatment groups.
Conclusion: The [17.1A × CD3] bispecific, with equal specificity to the parent immunoglobulin, but a unique ability to selectively recruit killer effector cells, can inhibit tumour growth *in vivo* and may prove an attractive adjuvant in high-risk colorectal cancer.

Poster 055

A randomized, blinded trial of home versus hospital administered phosphate enema as flexible sigmoidoscopy preparation

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Background: Preparation for flexible sigmoidoscopy is often achieved by administration of a phosphate enema by nursing staff in the endoscopy department, which is time consuming and often embarrassing for patients. This blinded, randomized trial aimed to compare adequacy of preparation and acceptability of home versus hospital-administered enema.
Method: Consecutive patients having flexible sigmoidoscopy were randomized to receive a phosphate enema as bowel preparation either in the endoscopy department or to self-administer the enema at home. Adequacy of preparation was recorded on a scale of 0 to 10, according to the percentage of mucosa visible. Operators were blinded to whether the enema was given at home or in hospital. After the examination patients were asked to complete a questionnaire on the ease of preparation.
Results: One hundred and twenty consecutive patients were recruited. Of the 56 patients offered home preparation 25 declined to self-administer the enema. Intubation to the descending colon or more proximally was achieved in 88, 88 and 84 per cent of those randomized to hospital preparation, declining and accepting home preparation, respectively. Bowel preparation scored 8·21 ± 1·72 (mean ± SD) in those patients randomized to hospital enema, 8·40 ± 2·02 in those declining home preparation and 9·19 ± 1·01 in patients self-administering the enema at home. There were no complications of flexible sigmoidoscopy during the study. Home enema patients often stated that they found home preparation easier or less embarrassing than previous hospital-administered enema.
Conclusion: Preparation of the left side of the colon is equally good whether the enema is administered by a nurse in the endoscopy department or by the patients themselves at home. Home preparation may lead to time and cost savings and be more acceptable to many patients.

Poster 056

Topical and oral diltiazem lower the resting anal sphincter pressure

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Background: This study aimed to investigate the effect of oral and topical diltiazem on lowering the resting anal sphincter pressure and to ascertain the most effective dosage and formulation.
Method: Two separate studies were conducted. In one study 10 subjects were given a placebo tablet followed by 60 mg diltiazem. Anal sphincter pressure and blood flow were measured before and 1 h after each tablet. Similar measurements were taken before, and 4 days after, once daily and twice daily regimens of diltiazem. In the second study diltiazem gels of increasing concentration were applied topically to the anus in 10 volun-

teers to determine the dose which most effectively lowers the resting anal sphincter pressure.
Results: 60 mg diltiazem lowered the mean resting anal sphincter pressure by 20 cm H_2O (21 per cent) compared to the pre-treatment value ($P = 0{\cdot}001$), whilst placebo was associated with a negligible 3 per cent decrease in the mean resting pressure ($P = 0{\cdot}09$). Once daily diltiazem produced no notable clinical effect whilst twice daily dosing reduced the mean anal pressure by 17 per cent ($P = 0{\cdot}008$). Two subjects noticed postural dizziness with this regimen. Topical diltiazem produced a dose-dependent reduction of resting anal pressure. A maximal effect was produced by 2 per cent diltiazem gel which lowered mean resting anal pressure by 28 per cent ($P < 0{\cdot}0001$), the effect lasting 3–5 h after a single application. Higher concentrations produced no additional effect. No side-effects were reported with topical diltiazem.
Conclusion: Both oral and topical diltiazem lower the resting anal sphincter pressure in healthy volunteers. Topical diltiazem seems both superior and safer than oral, with no side-effects encountered. It may therefore have a potential value in the treatment of anal fissures.

Poster 057

The efficacy of faecal diversion alone for extensive Crohn's disease

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Background: This study was to assess the efficacy of faecal diversion alone for extensive Crohn's disease. Furthermore, we examined whether it is possible to predict which patients will respond to it.
Method: Medical records of 39 patients who underwent faecal diversion alone for extensive Crohn's disease were reviewed.
Results: Faecal diversion alone (loop ileostomy: 33, loop sigmoid colostomy: 6) was attempted in 24 patients with extensive colorectal disease (10 with severe anal disease, and five severe small bowel disease). Nine patients (23 per cent) have gone into complete remission and have had no further surgery for Crohn's disease with a mean follow-up of 94 months, and among these nine patients, five underwent closure of ileostomy or colostomy. Nine patients (23 per cent) achieved remission for more than 24 months after faecal diversion, 12 (31 per cent) relapsed between 6 and 24 months, and nine (23 per cent) were not improved at all and required operation for Crohn's disease within 6 months. There were no patient characteristics which identified those who would enter long-term remission.
Conclusion: These data indicate that faecal diversion alone may have a profound effect in achieving remission in a few patients with Crohn's disease, but it is impossible to predict the outcome.

Poster 058

Risk factors for anastomotic recurrence after ileocolonic resection for Crohn's disease

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Background: This study was undertaken to investigate the factors that influenced the risk of anastomotic recurrence after ileocolonic resection for Crohn's disease.
Method: One hundred and forty-seven patients who underwent primary ileocolonic resection (ileocaecal resection or right hemicolectomy) between January 1980 and December 1995 were reviewed. Risk analysis was performed using Cox proportional hazard model and recurrence rates using Kaplan–Meier life-tables analysis.
Results: Only two factors emerged as being significantly related to anastomotic recurrence, these were: short duration of disease of less than 1 year prior to surgery (hazard ratio 4·23, $P = 0{\cdot}0005$) and smoking (hazard ratio 2·31, $P = 0{\cdot}002$). Age at onset of disease, sex, family history of Crohn's disease, perioperative corticosteroid therapy, emergency operation, type of disease (perforating/non-perforating), length of resected small bowel, length of resected large bowel, presence of granuloma in the specimen, involvement at the line of resection, or postoperative complications had no influence on anastomotic recurrence.
Conclusion: Short history of disease and smoking habit are important risk factors for anastomotic recurrence after ileocolonic resection for Crohn's disease.

Poster 059

Pruritus ani: experience from a combined colorectal and dermatological clinic

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Background: The aim of this study was to establish the cause of pruritus ani in a group of patients referred to a combined colorectal and dermatological clinic and determine the most appropriate treatment.
Method: Forty patients with pruritus ani were seen in a combined clinic over a 6-month period. Assessment was by history, completion of a general health questionnaire, full examination of the skin, digital rectal examination, proctoscopy, sigmoidoscopy and patch testing. Patients were treated according to clinical findings at assessment.
Results: Thirty-four patients (84 per cent) had a recognizable dermatosis, three (8 per cent) had superficial perianal fissuring and three (8 per cent) had a normal perineum; two cases (5 per cent) required surgical intervention. Twenty-two patients (55 per cent) had positive reactions when patch tested. All patients have shown an improvement or complete resolution of their symptoms with treatment.
Conclusion: This series has shown that the majority of patients presenting with pruritus ani have a dermatosis as the underlying cause of their symptoms and that many of them have developed contact sensitivities to the various topical medications used. These findings suggest that referral to a dermatologist in the first instance may be more appropriate.

Poster 060

Repair of multiple colonic perforations using skin staples in lieu of sutures

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Background: Serosally placed skin staples have been used in lieu of sutures to reduce the time taken to construct small intestinal and colonic anastomoses. This study evaluated the healing of experimental colonic perforations repaired with either skin staples or sutures, in the presence of peritonitis.
Method: At laparotomy 12 colonic perforations were created in the spiral colon of pigs ($n = 24$). After 6 h peritoneal lavage was performed and the perforations were closed, six by local excision and single-layer suture closure, and six by inversion and closure with skin staples. Animals were killed either immediately after repair, at 5 days or at 14 days. The integrity of repairs was assessed by intraluminal pressure testing at post-mortem.
Results: The time to complete the stapled repairs was significantly less than that for sutured repairs (mean ± SD time (minutes) for stapled repairs: 5·0 ± 2·1; for sutured repairs: 29·4 ± 4, $P < 0{\cdot}001$, ANOVA). Mean ± SD leak pressures (mmHg) of the repairs were:

	Group 1 (6 h, $n = 6$)	Group 2 (day 5, $n = 8$)	Group 3 (day 14, $n = 10$)
Stapled	225·3 ± 59·0	247·3 ± 54·3	177·6 ± 26·4
Sutured	193·2 ± 46·7	220·9 ± 71·2	183·4 ± 31·9

There was no significant difference in the leak pressures between repair techniques at any time point.
Conclusion: Colonic repair using either skin staples or sutures can be performed with safety in the presence of faecal peritonitis. The use of skin staples in lieu of sutures reduces operating time without reducing the biomechanical strength of the healing colonic wounds.

Poster 061

Defunctioning loop ileostomy: a worthwhile procedure

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Background: Defunctioning loop ileostomies are an uncommonly utilized form of faecal diversion. The aim of this study was to determine the morbidity associated with both construction and reversal of loop ileostomies.
Method: An analysis was performed of all patients undergoing loop ileostomy construction or reversal between 1990 and 1997.
Results: One hundred and two patients (43 male, 59 female) with a mean age of 38 (range 13–81) years had a loop ileostomy constructed. Indications for ileostomy construction included inflammatory bowel disease (76 patients), low anterior resection for carcinoma (16 patients) or miscellaneous reasons (10 patients). Nine patients (9 per cent) had complications arising from ileostomy construction including four parastomal infections, three high output ileostomies, one small bowel obstruction and one ileostomy stenosis in the early postoperative period. Only the stricture required surgical intervention. All other complications settled with conservative management. Mean time to ileostomy reversal was 16 weeks. Three patients (4 per cent) had complications associated with reversal. All of these complications required surgical intervention, two for small bowel obstruction, one for small bowel perforation. Currently 81 patients have had their ileostomy reversed, and 16 patients have had their loop ileostomy converted to a permanent stoma for reasons not related to the loop ileostomy itself.
Conclusion: Defunctioning loop ileostomy is associated with low morbidity. We recommend a defunctioning ileostomy as the procedure of choice for temporary faecal diversion.

Poster 062

A selective policy for surgery in rectal prolapse

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Background: Abdominal fixation for prolapse produces low recurrence rates but poor function. Rectopexy gives constipation; resection rectopexy may increase incontinence. Perineal operations are minimally invasive but have a high recurrence.
Method: We report 149 patients (133 females), mean age of 64 (±15) years with a median follow-up of 4 (0–9) years where surgery was selected on the basis of symptoms and general health. There were no operative deaths. Results shown below.
Results:

	Abdominal fixation	Perineal operation
No. patients	100	47
Prolapse recurrence	2 (2%)	8 (17%)
Constipation	51 (51%)	8 (17%)
Incontinence	52 (52%)	27 (57%)
Normal function	25 (25%)	6 (13%)

Conclusion: These data confirm that abdominal fixation is effective in preventing recurrent prolapse. Long-term functional results, however, are disappointing despite a selective policy; this may be related to the underlying pathophysiology of rectal prolapse.

Poster 063

The dose response of the internal anal sphincter to topical application of glyceryl trinitrate cream

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Background: Nitric oxide has been identified as an inhibitory neurotransmitter in the smooth muscle of the internal anal sphincter. The use of the nitric oxide donor glyceryl trinitrate in the treatment of high pressure anal disease such as anal fissure has created a great deal of interest. The dose response of the IAS to topical application of GTN cream, however, is still not clear. The aim of our study was to define the dose response to topical GTN on the IAS.
Method: A double-blind placebo-controlled dose-ranging study was carried out to compare the effect of three different concentrations of GTN cream (0·1, 0·2 and 0·4 per cent) on the IAS. Forty-eight patients were randomized and underwent ambulatory anorectal manometry using a two-port solid-state manometry catheter and ambulatory data logger. Patients had baseline manometry recorded for 1 h and then 1 ml of cream was applied to the anal canal. Patients underwent ambulatory anorectal manometry and recorded daily activities on an events diary. After 24 h the patients returned and the catheter was removed if not displaced by defecation. Data were down loaded and adverse events were recorded. Recordings were visually analysed for changes in mean anal pressure (MAP).
Results: Mean resting anal pressure for pre- and post-GTN treatment in cm H_2O is given below.

	Placebo	GTN 0·1%	GTN 0·2%	GTN 0·4%
Number	11	13	12	13
MAP Pre Rx	71·2	72·1	76·5	77·2
MAP Post Rx	64·2	56·00	54·5	50·2
GTN vs Placebo		$P=0·087$	$P=0·006$	$P=0·004$

Only three patients reported a mild transient headache on GTN application, these were distributed in all active treatment groups.
Conclusion: There is a significant drop in resting anal pressure after the application of GTN cream in all groups compared to placebo which appears to be related to concentration of GTN. In conclusion, the internal anal sphincter demonstrates a dose-related response to the application of the nitric oxide donor glyceryl trinitrate.

Poster 064

Laparoscopic-assisted mobilization of the gracilis muscle for dynamic anal neosphincter formation

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Background: The gracilis dynamic neosphincter performed as a two- or three-stage procedure is becoming increasingly established as a means of restoring continence in patients with end-stage faecal incontinence. Early morbidity is primarily due to sepsis, lead displacement or muscle/tendon failure. Morbidity due to long leg wound associated with gracilis mobilization is often described. We describe laparoscopic mobilization of the gracilis muscle as a modification of the gracilis dynamic neosphincter procedure.
Method: A 36-year-old woman underwent this modified procedure. Under general anaesthesia with hip joint in external rotation a 5 cm incision was made over the medial aspect of thigh 5–8 cm distal to pubic tubercle. A 10 mm Psion laparoscope with a 0 degree end-viewing lens allowed visualization of distal muscle mobilization with laparoscopic scissors without insufflation. Haemostasis was achieved by diathermy. A visiport with the laparoscope inserted for visualization was used to

complete distal dissection through a separate 2 cm incision. The rest of the procedure was done as per the standard technique of the surgeon. The laparoscopic section of the procedure took 62 min to perform and rest of the procedure, wrap and insertion of leads took 45 min. The patient mobilized 8 h after surgery.
Conclusion: We believe that gracilis can be mobilized safely by laparoscopic dissection. By using this approach, avoidance of a long leg wound with its attendant morbidity and early mobilization of the patient is possible.

Poster 065

ras pathways in colorectal cancer

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Background: The ras genes are key mediators of signal transduction controlling cellular proliferation and differentiation and between 25 and 50 per cent of colorectal cancers have been shown to have mutations in the Kirsten-ras gene which give rise to a constituatively active ras protein. This study was performed to examine whether other abnormalities of ras protein activation are present in colorectal cancers that do not have a Kirsten-ras mutation: in particular of growth factors and their receptors that signal via the ras pathway.
Method: Sections of 105 consecutive early colorectal cancers were obtained. DNA was extracted and mutations at codons 12 and 13 of the Kirsten-ras gene identified by direct sequencing. Immunohistochemical staining was used to identify expression of ras proteins, the growth factors EGF and TGF-α, and their common receptor, EGF-R.
Results: Of 105 colorectal cancers, 30 had activating mutations of the Kirsten-ras gene, 92 had high levels of ras protein, 84 produced excess EGF and 20 TGF-α, while 78 overexpressed EGF-R. Production of EGF and TGF-α were not mutually exclusive: 17 tumours produced both. EGF-R expression did not occur in isolation: 72 (92·3 per cent) also had high levels of ras protein and 71 (91 per cent) produced excess growth factor. There was no difference in growth factor, EGF-R or ras protein expression between wild-type tumours and those with Kirsten-ras mutations. However, a ras pathway abnormality was identified in over 95 per cent of the tumours.
Conclusion: ras pathway abnormalities are present in almost all colorectal cancers and may offer a suitable target for therapeutic intervention.

Poster 066

Long-term continence and pelvic floor injury

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Background: Obstetrically damaged anal sphincter is the principal cause of faecal incontinence in otherwise healthy women. The aims of this study were to assess the long-term outcome of obstetric pelvic floor injury. The incidence of faecal incontinence symptoms overall was 6·3 per cent and for urinary symptoms 8·2 per cent at 1 year.
Method: Obstetric and physiological data were prospectively collected in 159 women. We have reviewed the long-term symptomatic outcome of these patients at 1 year by questionnaire and physiological assessment correlated to postnatal scan.
Results: Ninety-nine out of the 159 replied (62 per cent). Of these patients, three (1·88 per cent) had new symptoms of faecal urgency, four (2·5 per cent) incontinence of flatus and two (1·25 per cent) incontinence of solid motions. Six (3·77 per cent) had new symptoms of urinary urgency, three (1·88 per cent) suffered with urinary stress incontinence and six (3·77 per cent) had urge incontinence of urine.

Endoanal scan result		Persistent new symptoms at 1 year		
Abnormal	15	Faecal	$n=2$	33·3%
		Urinary	$n=4$	26·6%
Normal	144	Faecal	$n=8$	3·47%
		Urinary	$n=9$	6·25%

Two patients had persistently low resting anal pressures and maximum squeeze pressures at 1 year, both had confirmed ruptured sphincters. One of these patients had incontinence of flatus and also urinary urge incontinence; the other was asymptomatic at 1 year.
Conclusion: The high-risk pelvic floor can be predicted by postnatal endoanal ultrasonography.

Poster 067

Hand-held manometry: a useful tool in the outpatient department

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Background: Does hand-held anal manometry transducer compare reliably with the standard pressure transducer used in the physiology department? Can the hand-held manometer be used as a convenient tool in the outpatient setting to avoid the need for a visit to the specialist anorectal physiology laboratory?
Method: Twenty-four patients were examined, four resting pressure recordings were recorded by each of the single channel hand-held pressure transducer (Gaeltec Ltd, Skye) and the dual channel pressure transducer with ambulatory box recorder MPR2 (Gaeltec Ltd, Skye) used routinely in the anorectal physiology laboratory. Maximum voluntary and involtunary pressures were also recorded.
Results: A total of 192 resting pressure recordings were analysed. Although individual records of pressure were not identical between the two groups, there was good correlation between corresponding hand and laboratory transducer readings per patient and between mean resting pressure readings. Maximum voluntary and involuntary pressures also correlate strongly (Spearman/Kendall non-parametric correlation and paired samples correlation).
Conclusion: The hand-held transducer is repeatable, and as good as the physiology laboratory equipment in measuring resting anal pressures. It is therefore useful in the outpatient department and as a research tool; avoiding the need for some patients to attend the anorectal physiology laboratory.

Poster 068

Expression of transforming growth factor beta polypeptides in colorectal cancer

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Background: Increased levels of the inhibitory peptide transforming growth factor beta 1 (TGFβ 1) in colorectal and other tumours are, paradoxically, predictive of poor prognosis. The aim of the present study was to determine the prognostic value of the TGFβ receptor (TGFβR2) and another TGFβ isoform (TGFβ 3).
Method: Expression of TGFβR2 and TGFβ3 was detected in 106 paraffin-embedded formalin-fixed colorectal tumour samples, by incubating three μ sections with either polyclonal anti-TGFβR2 (R&D Systems AF-241-NA) or anti TGFβ3 (R&D Systems AB-244-NA) antibodies after microwave retrieval. Specific antibody binding was detected with a biotinylated secondary antibody followed by an ABC peroxidase system (Vector Laboratories) using diaminobenazidine as substrate. The sections were counterstained with haemotoxylin. Cytoplastic staining was scored negative, positive or borderline when compared to control sections treated with a normal goat IgG instead of primary antibody.

Results: The survival analysis calculated using the Kaplan–Meier method is shown in the figure below.

	Negative staining		Positive staining		Borderline staining
Antibody	% of samples	median survival (weeks)	% of samples	median survival (weeks)	% of samples
Anti-TGFβR2	47	115	37	130	16
Anti-TGFβ3	37	99	54	112	15

Analysis of the survival curve showed that the presence of TGFβR2 ($P = 0{\cdot}82$) or TGFβ3 ($P = 0{\cdot}91$) was not predictive of survival.

Conclusion: Insenstivity to TGFβ1 is thought to be due to loss of signal transduction via the TGFβR2 and TGFβ3 has been shown to protect epithelial cells from cytotoxic and radiation damage. However, we could not demonstrate a correlation between the presence of TGFβR2 and TGFβ3 and survival in our cohort of colorectal tumours.

Poster 069

Crypt cell proliferation state in the human colon. Validation of results obtained by whole crypt microdissection and the findings in patients with familial adenomatous polyposis, sporadic adenomas and colorectal cancer

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Background: This study aimed to establish the validity of mitosis counts following whole crypt microdissection as an index of the crypt cell proliferative state (CCPS). To examine the effect of normal biological variables (age, sex and colonic site) and colonic neoplasia on the mitotic index in macroscopically normal human colon.

Method: Mucosal samples were obtained at colectomy or colonoscopy from 109 individuals (26 controls, 23 sporadic adenoma patients, 31 sporadic carcinoma patients and 29 patients with familial adenomatous polyposis [FAP]). The specimens were hydrated, hydrolysed and small groups of crypts separated from the main specimen under a dissecting microscope. The total number of mitoses/crypt were counted by one observer for each of 10 complete crypts.

Results: Validation work established that whole crypt mitoses counts were reliable and reproducible. There was no relation between age and mean mitoses/crypt (Pearson correlation coefficient −0·1). The CCPS count was higher for males than for females (M:F = 6·7:3·9, $P = 0{\cdot}008$) amongst the controls (but there was no gender difference in the three disease groups). The mean mitoses/crypt were similar for the controls and adenomas (5·6 and 4·7, respectively) but greater for the cancers and FAP (8·3 and 14·2, respectively). Statistical analysis confirmed that there were significant differences ($P < 0{\cdot}05$) between controls and all disease groups together, between sporadic disease and FAP and between adenoma and carcinoma subjects at each of the four colonic sites. For all disease groups and controls the crypt mitotic count showed a significant linear increase ($P \leq 0{\cdot}004$) from the rectum to the caecum. Biopsies from within 5 cm of the macroscopic margin of a carcinoma (near) gave a mean mitosis count of 12·6 whilst those from more than 10 cm (far) were lower but not significantly so ($P = 0{\cdot}12$) with a count of 9·0.

Conclusion: Whole crypt microdissection and mitosis counting is a reliable, reproducible and robust technique for assessing CCPS in the human colon. CCPS is unaffected by age, but increases from distal to proximal colon. CCPS is increased if a sporadic cancer is present and markedly increased in FAP. However, the precise relation of an increased CCPS to the neoplastic process remains uncertain.

Poster 070

Mesorectal excision for rectal cancer in a district general hospital

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Background: The aim of this study was to assess the results of mesorectal excision for rectal cancer in a district general hospital.

Method: All patients undergoing excisional surgery for rectal cancer under one surgeon from June 1991 to June 1997 reviewed retrospectively and partly prospectively.

Results: Eighty-one patients (45 male) with a mean age of 65·4 (range 38–87) years. Sixty-five procedures potentially 'curative' (i.e. no macroscopic residual disease/no perforation). Forty-one performed by the consultant and 24 by a higher surgical trainee assisted by the consultant. Forty-seven were anterior resections (30 defunctioned), 14 abdomino-perineal excisions, two Hartmann's, two procto-colectomies. All with mesorectal excision. Dukes' stage A 12 (18 per cent); B 22 (34 per cent); C 31 (48 per cent). Fifteen had preoperative radiotherapy, eight postoperative radiotherapy and 15 postoperative chemotherapy. Thirty-day mortality 3 (4·6 per cent). Clinically evident anastomotic leaks 3 (4·6 per cent), all in defunctioned anastomoses with no mortality/major morbidity. Of the 62 survivors in the 'curative' group, two (3·2 per cent) developed isolated local recurrence at 23 and 24 months postoperatively. Six developed distant recurrence (combined with local recurrence in one) at a mean of 16·7 months postoperatively (8–30 months). Mean follow-up 24·5 months (4–81).

Conclusion: Mesorectal excision for rectal cancer produces a low incidence of local tumour recurrence. It can be safely practised in the district general hospital setting by supervized higher surgical trainees.

Transplantation

Poster 071

Results of renal transplantation in Indo-asian recipients

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Background: In contrast to the results of renal transplantation into black recipients, the results of renal transplantation into Indo-asian recipients performed in the developed world have not been well studied. This unit serves a region with a large Indo-asian population and we have compared the results of renal transplantation in this group with those in our white population.

Method: Data were retrieved from our existing transplant database and by retrospective review of the case notes on all cadaveric transplants performed in the 9-year period to 31 December 1996. The results of transplantation in 49 Indo-asian recipients and 245 white recipients have been compared using non-parametric tests.

Results: There were no differences in median donor age (40 years for Indo-asians versus 41 years for whites, $P = 0{\cdot}88$), median recipient age (48 years versus 47 years, $P = 0{\cdot}68$), total number of mismatched antigens at HLA A,B and DR loci ($P = 0{\cdot}16$), median cold ischaemic time (23 h versus 20 h, $P = 0{\cdot}19$), or median anastomosis time (34 min versus 34 min, $P = 0{\cdot}97$). Postoperatively, immunosuppression was by cyclosporin-based dual therapy or triple therapy or by tacrolimus-based therapy in a small number of recipients. The quality of initial graft function was similar in both populations, with delayed graft function rates of 20 per cent versus 22 per cent and initial function rates of 80 per cent and 74 per cent for Indo-asians and whites, respectively. The incidence of acute rejection (biopsy confirmed) in the first 6 months was 29 per cent for Indo-asians and 37 per cent for whites ($P = 0{\cdot}35$). Rejection episodes were less commonly steroid resistant in Indo-asians than in whites but this difference just fails to reach statistical significance (5 per cent versus 16 per cent,

$P=0{\cdot}08$). Renal function as measured by median serum creatinine (µmol/l) was better in Indo-asians than in whites at 6 months, 1 year, 2 years and 5 years (140 versus 154, $P=0{\cdot}04$; 141 versus 155, $P=0{\cdot}05$; 133 versus 163, $P=0{\cdot}02$; 116 versus 157, $P=0{\cdot}002$). However, there was no difference in the graft survival between the two populations: 1 year 88 per cent for Indo-asians versus 81 per cent for whites, 2 years 83 per cent versus 77 per cent, 3 years 71 per cent versus 75 per cent, 4 years 64 per cent versus 70 per cent, 5 years 64 per cent versus 65 per cent.
Conclusion: We conclude that the results of renal transplantation into indo-asian recipients are at least as good as those in white recipients.

Poster 072

The brachiobasilic fistula is superior to prosthetic grafts for secondary vascular access

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Background: Patients requiring long-term haemodialysis often require multiple operations in order to maintain their vascular access. The options for secondary access procedures become increasingly limited as superficial veins become unavailable. Prosthetic grafts are commonly used in difficult cases but their use is associated with a high incidence of complications.
Method and Results: We have used the brachial artery-transposed basilic vein arteriovenous fistula in preference to prosthetic grafts in 31 cases where the superficial veins were not available. There have been no technical failures and 28 (90 per cent) of these fistulas have developed sufficiently to enable dialysis. No major infections have occurred. Three fistulas have been electively ligated because of steal phenomena or oedema. Two fistulas thrombosed but one was salvaged by thrombectomy and more proximal anastomosis. At median follow-up of 12 months, 24 fistulas remain patent. Prosthetic grafts have been used on 23 occasions since 1990. In four cases prosthetic conduits were used because the basilic vein was inadequate when explored. Three grafts could not be needled successfully. Fourteen grafts have thrombosed. Ten of these underwent emergency thrombectomy but flow was only successfully restored in nine. Eight grafts have become infected and have been removed. Three patients have died with functioning grafts. Grafts with 1 year follow-up ($n=16$) show only 43 per cent patency.
Conclusion: The encouraging results with the brachiobasilic arteriovenous fistula and the very disappointing results with prosthetic grafts suggest that, in difficult cases, the brachiobasilic fistula should be fashioned in preference to using prosthetic conduits wherever possible.

Upper Gastrointestinal

Poster 073

Cost effectiveness of laparoscopic surgery for gastro-oesophageal reflux disease

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Background: We studied our first 31 sequential patients undergoing laparoscopic Nissen fundoplication. In-theatre and in-hospital costs were calculated, based on £400 per hour and £150 per day, respectively. The cost of preoperative drug treatment was calculated, based on an annual cost of £460 per annum for 20 mg Omeprazole and £350 for 10 mg Cisapride t.d.s.
Method: Fifteen men and 16 women, mean age 45 (range 18–73 years). Median preoperative history of GORD 5 years (1–30 years). There were no conversions to open operation, no re-operation and no major complications. One patient was readmitted with recurrent symptoms within 1 week.
Results: Median in-hospital stay was 3 nights (range 1–8 nights). Median in-theatre time was 75 (range 50–180) minutes. Mean cost of in-patient care was £1300. Mean drug use 40 mg omeprazole; cost £921 per annum. Thirty of the 31 patients were able to abandon all anti-reflux medication postoperatively. The median De Meester symptom scores improved from 7 preoperatively to 1 postoperatively (range 9–1).
Conclusion: On this cost basis, cost of laparoscopic Nissen fundoplication is recouped within 18 months of operation, a significant saving on the NHS drug budget.

Poster 074

Helicobacter pylori in patients with familial adenomatous polyposis

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Background: Almost all patients with familial adenomatous polyposis (FAP) develop duodenal adenomas and approximately 5 per cent of these will go on to develop upper gastrointestinal cancer. The aim of this study was to detect the presence or absence of *Helicobacter pylori* in the gastric antrum of patients with FAP and document any association with of duodenal polyposis as *H. pylori* has been implicated in foregut neoplasia.
Method: Fifty FAP patients underwent upper gastrointestinal endoscopy. Biopsies of the gastric antrum were sent for histology and CLO test. An assessment of degree of duodenal polyposis was made.
Results: The median age was 40 years (range 22–66 years, 34 males). *H. pylori* was found in eight patients (16 per cent). In the patients greater than 40 years of age (30) significantly fewer were colonized with *H. pylori* than an age matched, asymptomatic group of the general population ($P<0{\cdot}01$). There was no correlation between degree of duodenal polyposis and presence or absence of *H. pylori*.
Conclusion: The incidence of *H. pylori* found in FAP patients was less than that of the asymptomatic general population. This may be related to the differences in the bile of these patients which may be having an inhibitory effect on the rate of *H. pylori* colonization. *H. pylori* does not seem to be implicated in their duodenal tumourigenesis.

Poster 075

Gastrostomy tube and button insertion at initial endoscopy

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Background: Endoscopic placement of a trocar and split sheath allows placement of either a gastrostomy tube or button, but tenting of the gastric mucosa hinders placement of the trocar. The aim of this study was to minimize the tenting effect.
Method: Following insufflation of the gastric cavity with a gastroscope a hollow cannula was placed directly into the gastric cavity (through the anterior abdominal wall) and a polydiosanone (PDS) thread passed down the cannula. Another cannula was placed 2–3 cm away through which a loop was passed. The PDS was placed through the nylon loop. The loop was closed and withdrawn with both cannulae through the anterior abdominal wall. Traction on the PDS lifted up both the abdominal wall and anterior aspect of the stomach. This allowed the trocar to be placed with a stab technique between the two threads. Postmortem porcine gastric studies ($n=10$) were performed to assess the amount of displacement of gastric mucosa with and without the PDS thread. Then the trocar and split sheath was inserted with a stab technique on a live porcine stomach ($n=10$).
Results: Postmortem studies showed: 1) displacement of gastric mucosa was significantly less ($P<0{\cdot}0001$, Mann–Whitney) when the PDS (median displacement was −0·5 cm, range −0·5 cm to 0·5 cm) was used than when no thread was used (median displacement 5 cm, range 3 cm to 5·5 cm). Traction on the gastric mucosa that is applied when a suture is used

results in a negative tenting effect; 2) the trocar was successfully placed in 100 per cent cases with the PDS but only in 50 per cent of occasions without PDS due to tenting ($P = 0.03$, Fisher's Exact test); 3) live porcine studies confirmed the easy placement of the trocar and split sheath with minimal tenting. This allowed placement of either a gastrostomy tube or button.

Conclusion: Placement of a trocar and split sheath is facilitated with this method allowing gastrostomy tubes and buttons to be placed at the initial endoscopy.

Poster 076

Helicobacter pylori and recurrence of ulcer-like pain after highly selective vagotomy

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Background: This study aimed to assess the association of *Helicobacter pylori* and recurrence of ulcer-like pain after highly selective vagotomy (HSV) for duodenal ulcer.

Method: A cohort of 433 patients who have had HSV in the last 6–23 years after HSV were asked to complete a questionnaire about their current symptoms and medication and offered 13C urea breath test for detection of *H. pylori*.

Results: Two hundred and twenty-seven patients, 175 men and 52 women, who have had HSV in the past (median age 38 years; range 18–66 years), replied to the questionnaire and undertook the 13C urea breath test. The urea breath test detected *H. pylori* in 146 patients (64·3 per cent). There were 83 patients (37 per cent) who experienced pain on most days or every day, or needed to take omeprazole, H_2 receptor antagonists or antacids on most days or every day. Fifty patients were positive for *H. pylori* and 33 were negative for *H. pylori*. The difference is statistically significant ($P < 0.0001$, Independent t-test).

Conclusion: *H. pylori* infection is present in 64·3 per cent of patients after HSV and may play a significant role in recurrence of ulcer-like pain.

Poster 077

Adenocarcinoma of oesophagus junction and cardia: similar response to neo-adjuvant therapy

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Background: There has been a major recent increase in the incidence of adenocarcinoma of the lower oesophagus, oesophago-gastric junction (OGJ) and gastric cardia, and it is unknown whether these tumours have a common aetiology and molecular tumourigenesis. Moreover, with multimodal approaches to therapy becoming standard for oesophageal adenocarcinoma, we set out to determine whether tumours of the OGJ and cardia respond similarly to multimodal therapy.

Method: We studied 63 patients with adenocarcinoma at these sites undergoing multimodality treatment (two cycles of fluorouracil and cisplatin and 40 Gy of external beam radiation). We classified patients as either responders (pathological T0N0-1, T1N0-1 or T2N0) or non-responders (T2N1 or T3N0-1).

Results:

	Cardia $n = 15$	OGJ $n = 24$	OES $n = 24$	
Responders	47%	58%	46%	$P = 0.64$
Complete pathological response	13%	33%	8%	$P = 0.07$
Nodes positive	27%	13%	38%	$P = 0.132$
3-year survival	33%	33%	25%	$P = 0.78$

Conclusion: There was no significant difference between the three tumour locations in terms of response to multimodal therapy, nodal status or survival, lending support to the thesis that these tumours share a common biology. Moreover, the inclusion of tumours from these three sites in trials of multimodality therapy appears valid.

Poster 078

Screening for gastric carcinoma using *Helicobacter pylori* serology

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Background: *Helicobacter pylori* infection is associated with a 3–4 fold increased risk of developing gastric carcinoma. It has been suggested that it may be possible to select patients who are at greater risk of gastric cancer for early endoscopy by serological testing for *H. pylori*. We wished to determine the prevalence of *H. pylori* infection, determined by two serological kits to maximize sensitivity, in patients presenting with gastric carcinoma in a University Teaching Hospital.

Method: One hundred and thirty-eight consecutive patients attending the surgical department from October 1990 to 1995 with gastric carcinoma (proven histologically) had 10 ml whole blood taken either preoperatively or no later than 2 weeks postoperatively. *H. pylori*-specific IgG assays were performed using both the Pylori Elisa II (BioWhitaker) and Premier *H. pylori* (Launch) enzyme-linked immunosorbent assay (ELISA) kits.

Results: We studied 138 patients with a median age of 70 years. Overall, the Launch kit was positive for *H. pylori* in 103 cases (74·6 per cent), and the BioWhitaker kit was positive in 84 cases (61 per cent; 10 cases equivocal). Concordance between kits was 81·9 per cent. If either kit was positive, 105 were *H. pylori*-positive giving a maximum sensitivity for detection of carcinoma of 76·1 per cent. The prevalence of *H. pylori* did not increase significantly in younger patients (21 of 28, 75 per cent patients aged <60 years versus 84 of 110, 76·4 per cent aged >60 years), in lower and mid-third tumours compared with upper third (42 of 55, 76 per cent; 19 of 26, 73 per cent; and 34 of 43, 79 per cent, respectively) or according to tumour stage (21 of 26, 80·7 per cent stage I; 9 of 14, 64·3 per cent, stage II; 38 of 43, 88·4 per cent stage III; and 37 of 55, 67·3 per cent stage IV, $P = 0.06$). Of the 33 patients that were negative for *H. pylori* on both kits, four had had previous gastric surgery and one had family history of gastric cancer, but no other risk factors could be identified.

Conclusion: At least 20 per cent of our carcinoma patients were negative for *H. pylori* using two ELISA kits. This approach cannot be recommended for prioritization of the investigation of dyspepsia.

Poster 079

Laparoscopic port site recurrence of cancer: a system of classification

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Background: The absence of a method of classifying port site recurrences (PCR) makes it difficult to collate and compare cases for descriptive, therapeutic and prognostic purposes. We attempted to provide a simple but practical classification based on the published case reports.

Methods: Through an extensive literature search and personal contacts, we identified 120 cases of PSR. We developed and sent a questionnaire to the authors, inquiring about details of the operation, the PSR and outcome of further intervention, without identifying case or source.

Results:

Type	Features
Type I	One PSR, usually at the port of specimen extraction or the working port. No other recurrences (13·0% of reported cases)
Type II	IIa One PSR plus a resectable intraperitoneal recurrence, usually in the vicinity of the bed of the resected viscus (e.g. paracolic gutter or gallbladder fossa). No peritoneal disease on first look procedure, no other recurrences on second (4·3%) IIb More than one PSR plus a resectable intraperitoneal recurrence (17·4%)
Type III	One or more PSRs in a patient with unresectable peritoneal nodules with or without ascites on second look only. No peritoneal disease on first look (34·8%)
Type IV	Any number of PSRs in a patient with unresectable disease (ascites, hepatic metastasis, carinomatosis peritonei) on first look (30·4%)

Conclusion: We believe this classification provides a useful framework for describing and comparing recurrences based on presentation and resectability. All 42 cases we have collected so far fall within these categories but 'atypical' cases may occur that warrant a slight modification to the above classification.

Poster 080

Rapid reduction of CO_2 causes laparoscopic aerosolization of free cancer cells: evidence from a new rat model

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Background: The mechanism of port site recurrence (PSR) following laparoscopy is unknown although the insufflatant is thought to contribute. We developed a new animal model to test the hypothesis that rapid reduction was more likely to aerosolize free cancer cells than slow reduction or gasless laparoscopy.
Method: We developed a novel portless gas reduction valve and randomized 55 Fischer rats into rapid reduction (RR, to receive 20 L CO_2 at 0·67 L/min, $n=20$), slow reduction (SR, 20 l at 0·44 L/min, $n=20$) and gasless control groups (GL, $n=15$). In half of the animals in each group (non-recovery) immunolabelled rat colon cancer cells (RCC2) were used and harvested peritoneal and port specimens examined by flow cytometry (FC) and fluorescence microscopy (FM) while in the other half (recovery) viable, unlabelled RCC2 were used and animals killed at 4 weeks.
Results: Nine of ten non-recovery RR animals had RCC2 on FM or FC compared to two in each of the SR and GL groups ($P=0·018$, Fisher's exact test). Two recovery RR animals developed PSR at 4 weeks compared to zero in the other groups ($P=0·315$).
Conclusion: In this simple model, dispersal of free cancer cells occurred by aerosolization during rapid reduction. This disseminated tumour into the general peritoneal cavity but was not a significant cause of PSR.

Poster 081

Gastric cancer in the over 80s: is radical surgery justified?

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Background: This study aimed to evaluate the outcome for patients over 80 years of age following surgery for gastric cancer.
Method: All patients who were diagnosed or treated for gastric cancer over a 5-year period (1990–1995) at our institution were reviewed. The results for patients over 80 years of age were analysed.
Results: Eighty-nine patients with gastric cancer over the age of 80 were identified (median age 82·8 years, range 80·2–92·6). Forty-seven (53 per cent) of these patients underwent a surgical procedure. Operative procedures included potentially curative (R0) resection (43 per cent), palliative (R1 or R2) resection (43 per cent), surgical bypass (9 per cent) or laparotomy/laparoscopy only (6 per cent). After potentially curative resection, in-hospital mortality appeared to be lower for patients operated on by the specialist upper GI team (2 of 13 patients) than by other surgical teams (3 of 7 patients) although this was not statistically significant (χ^2 $P=0·15$). Median survival of the whole group (89 patients) was 0·62 years. The overall survival for patients who underwent R0 resection by the upper gastrointestinal team was 58 per cent, 48 per cent and 19 per cent at 1, 2 and 3 years, respectively, with a median survival of 1·7 years.
Conclusion: Patients of advanced age can benefit from radical and potentially curative surgery for gastric cancer with acceptable perioperative mortality. Good results require careful case selection and preoperative staging and preferably treatment within a specialist unit.

Poster 082

Are patients with bleeding or perforated peptic ulcers being tested for *Helicobacter pylori*?

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Background: It is recommended that patients who have had surgery for bleeding or perforated peptic ulceration are tested for *Helicobacter pylori* in order to prevent further complications. Because it is often impractical to perform endoscopic antral biopsies either pre- or postoperatively, we have looked to see if these patients are actually being tested.
Method: From 1991 to 1997 all patients having surgery for bleeding or perforated peptic ulcer disease were identified from the operating theatre data base and the notes reviewed. Patients were sent questionnaires to determine symptoms.
Results: We found 83 patients with a mean age of 58 years (range 20–96 years); 51 of 61 patients were men. Only 21 of 83 patients were tested for *H. pylori*. Only 3 of 26 patients taking non-steroidal anti-inflammatory drugs (NSAIDs) and 2 of 13 patients who had an acid reducing operation were tested for *H. pylori*. Four patients were treated blindly. Patients were more likely to be tested if they were still experiencing symptoms but we found that 50 per cent of patients had been asymptomatic prior to the perforation or haemorrhage. Even after excluding patients on NSAIDs, who had acid reducing surgery, who were tested or had blind treatment, there were still 24 patients who could still benefit from *H. pylori* testing.
Conclusion: It is likely that a significant proportion of these patients are inadequately investigated and treated to prevent the risk of further complications.

Poster 083

The prognostic value of laparoscopic ultrasound identified lymph node status for patients with upper gastro-intestinal malignancy

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Background: We have previously shown that laparoscopy, combined with high frequency, high resolution ultrasound scan is a safe technique which improves staging of gastro-oesophageal malignancy when compared to conventional techniques (clinical, endoscopy, abdominal ultrasound and computed tomography [CT] scan). The aim of this study was to examine the impact on tumour recurrence and patient survival of intra-abdominal lymph node status as identified by laparoscopic ultrasound (LUS).
Method: Forty-four patients who had tumours, which were deemed resectable by the conventional staging modalities outlined above, and who underwent LUS, were available for follow-up. Of these, 37 had proceeded to resection and seven were managed by palliative therapies having been 'upstaged' by LUS. Data regarding LUS nodal staging, tumour recurrence

and patient survival were prospectively collected. All patients have been reviewed until death or at least 1 postoperative year. Nodal group comparisons are between tumours staged N0 compared with N1 or 2 by UICC criteria (1992).

Results: The overall group had a 58 per cent 1 year cumulative survival (median 14 months; standard error [SE] 0·08). However, those patients proceeding to resection had 67 per cent 1 year survival (median 17 months [SE 6]) which was much greater than the group that underwent palliative therapies, with no 1 year survivors (median 4 months [SE 6]). LUS-defined nodal status predicted no significant difference in survival of the overall group or gastric/oesophageal subgroups. However, there was a trend towards prolonged survival in the node-negative group (median 29 months; SE 9 in the node-negative group compared with 13 months; SE 4 in the positive group). Disease-free survival was greater in LUS node-negative patients (26 months [SE 2] compared with 13 months [SE 4], $P < 0·005$).

Conclusion: LUS staging allows us to predict the likelihood of recurrence of gastro-oesophageal malignancies. This may prove a useful tool for the appropriate allocation of patients to primary and adjuvant therapies

Vascular

Poster 084

An independent prospective audit of ruptured abdominal aortic aneurysms (AAA) in Wales

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Background: The aim of this study was to identify the incidence and mortality of ruptured abdominal aortic aneurysms (AAA) in Wales.

Method: All patients presenting to hospital with confirmed AAA rupture in Wales between September 1996 to February 1997 have been studied. Data were collected prospectively by the All Wales Audit Resource Unit observing strict confidentiality.

Results: Ninety-seven patients (64 men) with ruptured AAA were identified. Abdominal pain ($n = 55$), back pain ($n = 35$) and shock ($n = 71$) were the commonest presenting features. Associated risk factors included previous myocardial infarction ($n = 16$), angina ($n = 24$), hypertension ($n = 37$), stroke ($n = 13$), diabetes ($n = 7$) and smoking ($n = 29$) at the time of rupture. Sixty patients were referred from the accident and emergency department, 26 were referred directly by GPs. Eight were interdepartmental referrals and in three patients the route of referral was unknown. Fifty-eight patients were investigated by ultrasound/computed tomography scan prior to treatment. Twenty-five patients died without an operation (three dead on arrival, six in casualty and 16 unfit for operation). Operation was performed in 72 patients. Of those, 53 patients died within 30 days following operation. Complications following surgery included cardiac ($n = 14$), respiratory ($n = 12$), renal ($n = 6$) and stroke ($n = 1$).

Conclusion: Operative mortality was 74 per cent and the overall mortality for ruptured AAA reaching hospital in Wales was 80 per cent. Screening for AAA is probably the only way forward to improve these results.

Poster 085

The hidden hazards of blood transfusion during abdominal aortic aneurysm (AAA) repair: a comparison of autologous and homologous products

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Background: Cell-savers are increasingly used during AAA repair allowing autologous transfusion of red blood cells (RBC) in saline. However, the infusate may contain other constituents of whole blood and inadvertent transfusion of white cells, activated neutrophils (polymorphonuclear neutrophils [PMN] [$\times 10^9$/L]), lymphocytes (lymph), monocytes (mono), cytokines (interleukin [IL]-1, IL-6, IL-8, tumour necrosis factor alpha [TNFα] [pg/ml]), and lipid mediators (LTB_4 [pg/ml]) could promote a systemic inflammatory response syndrome.

Method: Thus levels of these mediators were measured in 10 patients during AAA repair, in the infusate from a cell-saver and in 10 units of homologous packed-cells (values are medians and interquartile ranges).

Results:

	Patient	Infusate	Packed cells
WBC	5·55 (4·60–7·10)	5·65 (4·70–6·15)*	7·20 (5·90–8·55)†
PMN	4·40 (3·38–5·42)	4·25 (4·05–4·95)	2·30 (0·75–3·55)*†
Mono	0·14 (0·09–0·16)	0·14 (0·10–0·21)	0·80 (0·60–1·40)*†
Lymph	1·20 (0·91–1·32)	0·90 (0·62–1·65)	4·90 (3·60–6·20)*†
CD11b	160 (132–256)	538 (353–1131)*	875 (689–938)*
CD18	117 (105–131)	194 (148–228)*	199 (153–210)*†
L-selectin	59·6 (46·8–61·5)	51·8 (35·3–74·8)*	232 (157–241)*†
LTB_4	7·15 (4·20–10·55)	264 (129–480)*	56 (36·5–164)*†
IL-6	20·15 (17·75–24·85)	39·05 (24·25–100)*	4·65 (4·60–5·0)*†
IL-8	1·00 (0·25–3·00)	10·50 (5·10–27·05)*	14·00 (9·65–26·00)*

*$P < 0·0001$ versus patient, †$P < 0·0001$ packed cells versus infusate, minimal IL-1 and TNF-α detected in both products.

Conclusion: The infusate contains activated PMN (increased CD11b and CD18 expression, L-selectin shedding), monocytes and lymphocytes, and increased levels of LTB_4, IL-6 and IL-8. Theoretically the transfusion of these factors may be deterimental. Although similar results were obtained from homologous packed cells this contained greater numbers of cytokine producing monocytes and lymphocytes. This, and the other clinical advantages of autologous blood transfusion, favour the continued use of cell-saver devices.

Poster 086

The cytokine response to controlled reperfusion during limb salvage surgery

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Background: Neutrophils (PMN) promote ischaemia-reperfusion injury (IRI) and PMN depletion by both mechanical and immunological methods has been shown to ameliorate this injury in animal models. However, thus far leucodepletion has not been subjected to clinical assessment.

Method: In 10 patients undergoing limb salvage surgery, the effect of PMN depletion (using a double lumen femoral venous catheter, extracorporeal circuit, leucocyte filter, and flow rates of 200 ml/min for 15 min [3000 ml or ~60 per cent blood volume filtered]) upon levels of interleukin (IL)-6, IL-8 and tumour necrosis factor alpha (TNFα) were compared with the same measurements in 10 control patients undergoing similar surgery (CP). Samples were taken from both peripheral (PER) and femoral (FEM) venous blood at baseline, reperfusion (T_0), 4 h, 24 h, 3 and 6 days (T_4, T_{24}, T_{3D}, T_{6D}).

Results: Except at baseline, levels of IL-6 were lower in the filter patients (FP) at all time points. These differences (expressed as percentage changes from baseline, median and interquartile ranges) were significant at T_0FEM (FP versus CP: +122 per cent versus +148 per cent, $P < 0·0001$), T_0 PER (FP versus CP: +15 per cent versus 52 per cent, $P < 0·0001$), T_{3D} (FP versus CP: +79 per cent versus +444 per cent, $P = 0·0256$), T_{6D} (FP versus CP: −24 per cent versus +221 per cent, $P = 0·0457$). TNFα levels were higher in FP, particularly at T_0 PER (FP versus CP: −15·7 per cent versus −16·8 per cent, $P < 0·0001$) and T_4 PER (FP versus CP: −9 per cent versus −43 per cent, $P < 0·0001$). Levels of IL-8 were lower in the PER samples [T_0(FP versus CP: +1·8 per cent versus +4·1 per cent, $P < 0·0001$), $P < 0·0001$), T_{24}(FP versus CP: +2 per cent versus +125 per cent, $P < 0·0001$)] but higher in FEM samples [T_4(FP versus CP: +24 per cent versus +5 per cent, $P < 0·0001$) T_{24}(FP versus CP: +72 per cent versus +49 per cent, $P < 0·0001$)] of filtered patients.

Conclusion: This study of intraoperative PMN depletion showed changes in the cytokine profile that would be consistent with amelioration of IRI. Thus levels of the PMN-dependent pro-inflammatory cytokine IL-6 were reduced, whilst those of IL-8 in femoral blood increased (leucocyte adhesion inhibition effect). Similarly peripheral TNFα levels were higher and this should suppress PMN release from bone marrow reserves. The incidence of infective complications, amputations and death were comparable in the two groups. This technique appears safe, and its therapeutic role warrants further investigation.

Poster 087

An evaluation of the elastic properties of *in situ* human umbilical vein grafts

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Background: Compliance mismatch between an artery and graft leads to a region of excessive mechanical stretch with endothelial injury and flow disturbance. These factors are known to be involved in the development of intimal hyperplasia around anastomoses, with associated implications on graft patency. The aim of this study was to determine the elastic properties of the human umbilical vein (HUV) graft *in vivo* and compare them with the recipient's vessels (artery proximal and distal to the anastomosis).

Method: Forty grafts used for femoropopliteal bypass were assessed by duplex imaging with simultaneous blood pressure monitoring. Distension and diameter of the vessel or graft with a certain pressure change were used to calculate relative distension (RD), distensibility coefficient (DC), and compliance coefficient (CC). Data are expressed as median with interquartile range.

Results:

	Proximal artery	HUV graft	Distal artery
RD (%)	4·58 (2·48–6·85)	5·6 (3·4–10·95)	4·7 (2·35–8·90)
DC (10^{-3}/kPa)	9·75 (5·62–14·40)	13·00 (8·45–24·65)	9·2 (5·05–21·80)
CC (mm^2/kPa)	0·94* (0·43–1·77)	0·55 (0·34–0·70)	0·37 (0·19–0·61)

*$P<0·01$ when compared with graft or artery using Mann–Whitney U-test.

There was no significant difference between the RD or the DC, between the host artery and the HUV graft. The HUV graft was then compared with a series of 12 patients with *in situ* saphenous vein grafts and no significant difference in RD, DC or CC was found between the two groups ($P=0·42$).

Conclusion: This study demonstrates the elastic properties of the HUV graft *in situ*. It has similar properties to native artery and *in situ* saphenous vein grafts and may therefore have theoretical advantages over other prosthetic conduits.

Poster 088

Prevalence of visceral artery disease in patients undergoing renal revascularization

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Background: The choice of renal revascularization procedure is influenced by the site of the stenosis, the patency of the contralateral renal artery and the presence of visceral artery disease, particularly of the coeliac axis. In this study, we reviewed the prevalence of contralateral renal artery stenosis, superior mesenteric artery stenosis and coeliac axis stenoses in patients who had undergone renal revascularization.

Method: The angiograms of 122 patients (57 renal angioplasties and 65 anatomic and extra-anatomic bypasses performed between 1992 and 1997) were reviewed.

Results: All patients had renal artery stenosis of greater than 50 per cent. Renal artery occlusion was present in 30 per cent of patients, 10 per cent were bilateral. The prevalence of contralateral renal artery stenosis (>50 per cent) was 64 per cent. Stenoses in either the superior mesenteric artery (SMA) or coeliac axis (CA) were present in 67 per cent of these patients. Stenosis on the CA were the most frequent (60 per cent of all patients). Stenoses of all four vessels (both renal arteries, SMA and CA) were present in 23 per cent.

Conclusion: This study demonstrates the frequent co-existence of coeliac axis and contralateral renal artery stenoses. Screening of all visceral vessels with lateral views of the origins of both SMA and CA is recommended for the appropriate choice of renal revascularization procedure.

Poster 089

Endovascular stents in aortoiliac disease: a single centre experience

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Background: This study aimed to evaluate the initial and late results of intravascular stenting for atherosclerotic occlusive disease of the aortoiliac region and to determine potential predictive factors of stent failure and success.

Method: The preprocedural clinical records, ankle:brachial pressure index (ABPI), duplex and angiographic data were assessed on 140 patients (162 limbs) who underwent primary or secondary stent placement for lesions in the common iliac (55 per cent) or external iliac (45 per cent) artery, either for an occlusion (61 per cent) or stenosis (39 per cent). Initial and late success was assessed by restoration of femoral pulse, Fontaine score and ABPI and, where available, by duplex and angiography. A further cohort of patients at 1 year underwent duplex assessment.

Results: Clinical follow-up data (mean 18 months) were available for 125 patients (93 per cent). In this cohort improvement at last follow-up was determined by: Fontaine criteria (71 per cent); patient reported claudication distance (89 per cent) and ABPI measurement (97 per cent). Primary patency as assessed clinically, for occlusions was 90 per cent at 1 year and 89 per cent at 18 months and for stenoses was 94 per cent at 1 year and 94 per cent at 18 months. Absent femoral pulses were restored in all cases ($n=100$). Technical problems included failure to place stent, eight cases (4·4 per cent), unsatisfactory stent placement, 13 cases (8 per cent) and persistent gradient, 16 cases (10 per cent). Early complications occurred in seven patients (4 per cent) and included one death, two episodes of distal embolization, one amputation and three cases of thrombosis. Late complications of stent restonosis and occlusion occurred in 13 patients (8 per cent) and one case of stent migration. More occlusive lesions (9/100) were subject to late complications than stenoses (4/62). Other significant factors included lesions of the common iliac artery, persistent gradient, incorrect placement, continued smoking, not on antiplatelet agents and male gender ($P<0·05$ χ^2). Use of multiple stents favoured long-term patency ($n=20$, $P<0·05$).

Conclusion: Stenting of the iliac arteries is safe and durable stenting can be equally applied to occlusions as well as stenoses with similar early and immediate results, and only a slightly increased incidence of late failure.

Poster 090

Quality control during endovascular aortic surgery: role of sac pressure and lower limb Doppler measurements

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Background: Endovascular aneurysm repair is associated with technical failure of stent deployment in up to 10 per cent of cases. The aim of this study was to employ direct measurement of the aneurysm sac pressure and Doppler flow monitoring of the superficial femoral artery (SFA) to ensure complete exclusion of the aneurysm from the circulation.

Method: An angiographic catheter was passed via an ilio-femoral conduit into the aneurysm sac of 14 consecutive patients undergoing endovascular aorto-uni iliac repair. This catheter was connected to an external pressure transducer allowing pressure monitoring during, and for 24 h post-procedure. Flow was monitored in the SFA by insonation with a 2 MHz Doppler ultrasound probe.
Results: No technical defect was observed in the deployment of 9 of 14 stents where there was marked reduction in sac pressure and good flow in the lower limb (results show the median and range of aneurysm sac pressure as a percentage of systolic blood pressure):

	Pre-deployment	Post-deployment	Completion	24 h postoperative
Pressure	112 (95–124)	57 (35–86)	42 (34–75)	55 (27–76)

In five cases technical problems were detected by the monitoring process. In three cases incomplete stent deployment was detected by a rise in sac pressure to systolic pressure after balloon deflation. In a further two cases the aneurysm sac pressure rose towards completion. Poor SFA flow was detected in one and contrast injected into the aneurysm sac revealed incomplete iliac occlusion, requiring open ligation. The second had good SFA flow and contrast injection revealed large patent lumbar vessels. Contrast injection at 24 h revealed complete exclusion of the sac. Two patients required conversion to open repair.
Conclusion: Monitoring aneurysm pressure in combination with SFA Doppler flow can detect complications of endovascular aneurysm repair which can be corrected intraoperatively.

Poster 091

Thrombelastography: an effective screening test for prothrombotic states

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Background: A proportion of the population have an inherited thrombotic tendency predisposing to fatal thromboembolic disorders. Their investigation is expensive and often only undertaken in specialist centres. Thrombelastography (TEG) is a method of global haemostasis testing. It is a cheap, easy test to perform. Over 15–30 minutes a characteristic tracing is developed from measuring the strength of the clot as it forms.
Method: One hundred and three consecutive patients who were attending for investigation of a suspected prothrombotic state were analysed by TEG in addition to standard thrombotic screening tests. TEG results were blindly analysed and stratified into normal, hypocoaguable, hypercoaguable or borderline. Comparison was made of the interpretation of the two sets of results (TEG versus thrombotic screening tests).
Results:

	TEG results			
Blood test results	Normal	Hypocoaguable	Hypercoagulable	Borderline
Normal	31	3	10	8
Abnormal	0	4	15	16
Anticoagulants	0	16	0	0

All patients normal on TEG were found to be normal on thrombotic screening. Twenty of 23 (87 per cent) identified as hypocoagubale had an identifiable cause, either warfarin therapy or factor XII deficiency. Thirty-one of 49 (63 per cent) patients identified as borderline or hypercoaguable had a defined prothrombotic abnormality. Eighteen patients were shown to be hypercoaguable or borderline by TEG but no prothrombotic abnormality was found.
Conclusion: The TEG is a simple and rapid test to perform. Patients identified as hypercoaguable or borderline merit formal investigation for an underlying prothrombotic abnormality. A normal TEG obviates the need for formal investigation in approximately one third of patients

Poster 092

Outcome following stenting for aortoiliac occlusive disease

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Background: The aim of this study was to determine the outcome of patients undergoing stent insertion for aortoiliac occlusive disease.
Method: Thirty patients who had stent insertion over 3 years were reviewed. Eight patients underwent stenting of bilateral lesions, giving a total of 38 lesions treated. Twenty-two lesions were treated for claudication, 16 for critical limb ischaemia (10 rest pain, six ulcers and two gangrene). Indications for stenting were complete occlusion (22), severe primary stenosis (15) and restenosis (1). Thirty of the lesions were in the common iliac, and eight in the external iliac artery. There were 13 Palmaz, 13 Wallstents, 10 Memotherm and two Symphony stents inserted.
Results: There were two early stent occlusions, at day 2 and day 7, both in patients with critical limb ischaemia. Both these patients required eventual limb amputation (1 above knee amputation, 1 below knee amputation). One patient died of respiratory failure on day 15 after stent insertion unrelated to the stenting procedure. There were two groin haematomas. Adjunctive procedures included thrombolysis in one patient, percutaneous angioplasty distal to stent insertion in two patients and infra-inguinal bypass grafting in four patients. One patient required embolectomy due to a complication of stent insertion. Thirty-one of the 38 stents (82 per cent) were patent at mean follow-up of 12 (range 1–33) months.
Conclusion: Stenting for iliac occlusive disease can be performed with acceptable early complication rates. Early patency rates are encouraging.

Poster 093

Elective repair of type IV thoraco-abdominal aortic aneurysms: experience with a subcostal transabdominal approach

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Background: Univariate analysis of preoperative factors in 74 type IV thoraco-abdominal aortic aneurysm (TAAA) repairs revealed that preoperative pulmonary function tests provided the only significant predictor of postoperative morbidity. A technique using a subcostal approach was first proposed in 1995. We now review the results of this technique with particular emphasis on outcome and changes in early postoperative pulmonary function.
Method: A single surgeon performed 62 elective type IV TAAA repairs from which full clinical and respiratory data was available in 35: 20 thoraco-laparotomy (Group I) and 15 transabdominal (Group II).
Results: The overall 30-day mortality was 11·4 per cent (four patients). No patient developed paraplegia or required long-term renal support. No significant differences were seen in age, weight, anaesthetic time or recorded blood loss between the two groups.

	Group I	Group II
Standardized preoperative PEFR	73%	80%
Standardized preoperative FEV1	83%	89%
Standardized preoperative FVC	92%	89%
ITU admission FiO2	0·45	0·58
ITU admission pO2 (kPa)	11·7 (6·5–28·6)	7·1 (7·3–24·8)
ITU admission pCO2 (kPa)	5·20 (4·1–7·2)	5·14 (3·7–8·8)
Intubation (h)	19	11
ITU stay (days)	2 (median)	4 (median)
Ward stays (days)	12 (median)	11 (median)

The only difference to reach significance was in ITU admission FiO2 ($P=0{\cdot}07$). Splenic injury (4 of 15 versus 2 of 20) and re-operation (5 of

15 versus 0 of 20) were more common in Group II patients. Weight was a significant predictor for re-operation in Group II patients ($P = 0{\cdot}05$).

Conclusion: The overall morbidity and mortality were acceptable. The higher rates of splenic injury and re-operation in the subcostal group suggest that they may have been presdisposed to by technical problems resulting from restricted access. The association between the likelihood of re-operation and weight is consistent with this view. Any benefit in improved respiratory function has been outweighed by an increase in complications, possibly the result of technical problems due to lack of good exposure.

Poster 094

Critical limb ischaemia in patients with end-stage renal failure

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Background: The study aimed to assess the mortality and limb salvage rate for critical ischaemia in patients with end-stage renal failure.

Method: Thirty-one patients with 37 critically ischaemic legs presented over 18 months; male:female ratio 22:9, mean age 63 (range 32–85) years. There were 21 diabetics (68 per cent), 24 patients on dialysis (77 per cent) and seven had a functioning renal transplant (23 per cent). Twenty-three patients (62 per cent) had rest pain, 21 (57 per cent) ulceration and 22 (59 per cent) gangrene.

Results: Arterial revascularization was performed in 23 of 37 legs (59 per cent). This included seven angioplasties, 14 infra-inguinal grafts (two above knee, five below knee and seven crural) and one graft thrombectomy. Successful limb salvage was achieved in 15 of 22 revascularized limbs (68 per cent) but four limbs required minor foot amputations at the time of surgery. The other seven required a major amputation (32 per cent), five below knee and one above knee. Fifteen out of 37 limbs (41 per cent) in 13 patients were unsuitable for revascularization. Of these, five had a minor foot amputation only and retained a functioning limb, two died with critical ischaemia and eight had a major amputation (seven below knee and one above knee). The 30-day mortality for these patients was 3 of 31 (10 per cent). During a mean follow-up of 8 months 7 of 31 patients died (23 per cent).

Conclusion: Primary amputation is more common in patients with critical limb ischaemia and end-stage renal failure, but for those in whom revascularization is undertaken the results are worthwhile for this severely handicapped group of patients.

Poster 095

The prevalence of cerebral computed tomography infarction in the asymptomatic carotid surgery trial in relation to carotid stenosis and prior contralateral symptoms

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Background: The Asymptomatic Carotid Surgery Trial (ACST) has randomized over 1670 patients to determine if carotid endarterectomy prolongs stroke-free survival versus best medical treatment alone. This study aimed to determine the prevalence of hemispheric cerebral infarcts in relation to severity of ipsilateral carotid disease and prior contralateral symptoms.

Method: Patients with preoperative computed tomography (CT) were divided into groups with ipsilateral stenoses >80 per cent or <80 per cent and into groups with prior contralateral stroke, cortical transient ischaemic attack (TIA), amaurosis fugax or no symptoms.

Results: There were 1144 patients with preoperative CT and 170 patients with MR scans. Patients with bilateral carotid stenosis >80 per cent (41 of 524) by duplex had a higher prevalence of cerebral CT infarction (37 per cent versus 18 per cent, $P = 0{\cdot}03$) compared to patients with unilateral stenosis >80 per cent (483 of 524). Patients with unilateral stenoses >80 per cent (483 of 1609) had a higher prevalence of ipsilateral CT infarction (18 per cent versus 13 per cent, $P = 0{\cdot}01$) compared with unilateral stenoses <80 per cent (1126 of 1609). Those with prior contralateral stroke (134) had the highest prevalence of hemispheric CT infarcts (61 per cent). Those with TIA (122) had a 30 per cent prevalence of CT infarction. Prevalence of hemispheric CT infarcts was 18 per cent in patients with amaurosis fugax (45) and 10 per cent in those with no prior symptoms (758). The Mantel– Haenszel test for linear association was significant ($P < 0{\cdot}001$) for increasing severity of symptoms.

Conclusion: In the ACST, patients with bilateral or unilateral carotid stenosis >80 per cent had a higher prevalence of cerebral infarction. The prevalence of contralateral hemispheric infarction was proportional to the severity of prior contralateral symptoms.

Poster 096

A comparison of transcranial Doppler and transcutaneous cerebral oximetry to stump pressure measurements during carotid endarterectomy

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Background: Transcutaneous cerebral oximetry (TCO) and transcranial Doppler (TCD) monitoring can be employed during carotid endarterectomy (CEA) to determine changes in cerebral perfusion during clamping. The aim of this study was to compare TCO and TCD with carotid stump pressure measurements.

Method: Thirty patients undergoing CEA were studied. Ipsilateral cerebral oximetry and TCD monitoring of the ipsilateral middle cerebral artery (MCA) were performed. After carotid clamping, the mean carotid stump pressure was measured. The percentage fall in MCA velocity and the fall in cerebral oxygen saturation were also recorded.

Results: Patients were divided into those with a stump pressure >50 mmHg (18) and those with ≤50 mmHg (12). The median fall in MCA velocity when stump pressure was >50 mmHg was 31 per cent. Median fall in MCA velocity when stump pressure was ≤50 mmHg was 51 per cent. There was a significantly larger fall in MCA velocity when stump pressure was ≤50 mmHg ($P = 0{\cdot}01$ Mann–Whitney U-test). The fall in MCA velocity inversely correlated with the ratio of stump pressure to mean arterial pressure (Spearman, $r = 0{\cdot}77$, 95 per cent CI: 0·90 to 0·48, $P < 0{\cdot}0001$). The fall in cerebral oxygen saturation was not associated with mean stump pressure ($P = 0{\cdot}2$). The fall in oxygen saturation was inversely correlated with the ratio of stump pressure to mean arterial pressure (Spearman, $r = 0{\cdot}55$, 95 per cent CI: 0·83 to 0·06, $P = 0{\cdot}03$). There were no postoperative neurological events in the study.

Conclusion: The measurement of MCA velocity by TCD may be a useful adjunct to stump pressure measurement in deciding when to use a shunt as well as for shunt monitoring. Cerebral oxygen saturation may not be as comparable, casting doubt on its usefulness in clinical practice.

Poster 097

Quantitative reflux measurements before and after surgical treatment of varicose veins

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Background: The aim of the study was to determine the amount of reflux in limbs with incompetent veins both pre- and postoperatively in order to demonstrate effective treatment.

Method: Sixteen legs of 12 women with varicose veins were included in this prospective study. The level of the saphenofemoral junction ± the incompetent perforating veins were marked preoperatively with duplex scanning. The venous filling index (VFI) denoting the amount of reflux in

ml/s was measured by air-plethysmography (APG) the day before the operation and on day 1 and at 6 weeks postoperatively.
Results: With APG the mean amount of reflux preoperatively was 4·11 ml/s, (min 2·4; max 7·8). On day 1 postoperatively the VFI normalized (i.e. less than 2·0 ml/sec) in all but five patients (mean value 1·76 ml/s). At 6 weeks postoperatively the mean value of the VFI was 1·54 ml/s. In the two limbs that the VFI remained greater than 2 ml/s the preoperative values were 5·1 and 7·8 ml/s and were reduced to 3·9 and 2·4 ml/s, respectively. The first patient had additional short saphenous vein incompetence that was not corrected.
Conclusion: Air-plethysmography is a valuable test that quantifies the amount of reflux in ml/s preoperatively and could be used for the postoperative documentation of effective treatment of limbs with incompetent veins. This could be particularly valuable in patients with intractable ulcers and to monitor the long-term results of valvuloplasty operations.

Poster 098

Endovascular repair of abdominal aortic aneurysms: improved access with iliac arterial wallstents

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Background: Iliac arterial tortuosity and luminal narrowing can cause problems during insertion of bifurcated aortic stent grafts with possible limb occlusion. We aimed to review the effect of prophylactic iliac stenting on the outcome of abdominal aortic aneurysm (AAA) stent grafts and associated radiological exposure.
Method: Between December 1995 and October 1997, 40 patients underwent endovascular treatment of infrarenal AAAs. In all cases a bifurcated device was successfully deployed. Nine patients were noted to have an iliac stenosis or narrowing with significant tortuosity. Wallstents were placed in the iliac vessels of all nine patients (seven unilateral, two bilateral) prior to insertion of the aortic stent. Follow-up was by computed tomography at 1, 3, 6, 12, 18 months (median 6; range 1–21 months).
Results:

	Wallstent	No wallstent	*P*
Number	9	27	
Median fluoroscopy time	27 min	32 min	NS
Median contrast volume used	350 ml	290 ml	NS

Two early and two late iliac limb occlusions have occurred, none in the group pre-treated with wallstents. One early occlusion occurred during treatment of a proximal endoleak. The remaining three have all been associated with significant iliac angulation (>80°). There were no procedural deaths or conversion to open repair. One patient pre-treated with a wallstent died on day 6 from a myocardial infarct. Of the remaining eight patients, all have patent iliacs bilaterally, no endoleaks and no distal complications. Overall 30-day mortality = 5 per cent (11·1 per cent for the wallstent group).
Conclusion: A high proportion of bifurcated stent grafts will occlude at least one limb in the presence of iliac tortuosity or stenosis. Wallstents appear to decrease this occlusion rate without significantly increasing radiological time, allowing easier stent graft deployment.

Poster 099

The impact of aortic stenting on aneurysm mortality

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Background: Between 1988–1992, the perioperative mortality for elective abdominal aortic aneurysm (AAA) repair at this hospital was 3·9 per cent. Our aim was to examine the impact of an aortic stenting programme on mortality rates for patients undergoing elective AAA repair.
Method: Between December 1995 and September 1997, computed tomography (CT) and calibrating arteriography were used to select patients for aortic stent graft repair. Standard open repair was performed for those unsuitable for stenting. Results were recorded prospectively on a computerized vascular data base (BIPAS) and mortality compared.
Results:

	n	No. deaths	Perioperative mortality rate
Stent grafts	37	2	5·4%
Open repair	70	9	12·8%
Total	107	11	10·2%

Conclusion: The 30-day mortality for the repair of elective infrarenal AAAs has risen three-fold over the last 5 years but these figures reflect both alteration in referral patterns and patient selection for elective surgery. It is misleading to compare the results of aortic stenting with either historical or consecutive groups of patients undergoing open AAA repair. The true impact of aortic stenting on perioperative mortality will not be known until the results of multi-centre randomized prospective trials are available.

Poster 100

Are early results of abdominal aortic aneurysm stenting misleading?

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Background: If abdominal aortic aneurysms (AAA) fail to decrease, or actually increase in size following stenting, there may still be a risk of rupture. Our aim was to examine early changes in AAA size following apparently successful aortic stenting.
Method: Forty AAAs have been repaired using a bifurcate system. The maximum aortic diameter was recorded for each patient on preoperative computed tomography (CT). Follow-up scans have been performed at regular intervals (0, 1, 3, 6, 12 and 18 months). All scans have been examined for endoleak and change in AAA diameter. Patients have been grouped dependent upon initial AAA size (Group 1, 45–54 mm; Group 2, 55–64 mm; Group 3, >65 mm).
Results: Two patients died prior to discharge. Thirty-three patients have reached 1 month follow-up (median 6 months; range 1–21 months). Changes in AAA diameter are shown as percentage of the immediate postoperative measurement (giving median values and ranges).

	Group 1	Group 2	Group 3
Number of patients	11	14	8
Median follow-up (months)	6	6	6
% diameter change	−4·3% (−28·8 to +1·5)	−2·4% (−30 to +8·3)	−2·4% (−15·6 to +4)

Since stent insertion, 20 aneurysms have decreased, seven increased and six remained unchanged in size. Two aneurysms have increased by greater than 5 per cent but neither has an endoleak evident on CT.
Conclusion: Despite an apparently successful procedure, CT has revealed shrinkage of the sac in only 61 per cent of patients and AAA diameter has actually increased in 21 per cent. These patients may have small endoleaks undetected on CT and interpretation of 'stenting success' should be guarded until long-term results are available.

Poster 101

Modular bifurcate aortic stent grafts

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Background: This study aimed to assess the mid-term results of the Vanguard aortic stent grafts (ASG) for the treatment of abdominal aortic aneurysms (AAA).
Method: Over 28 months, 371 AAAs have been assessed using computed tomography (CT). Calibrating angiography was performed on 129, of which 64 were repaired using a Vanguard ASG. Patients have been followed-up clinically and with regular contrast-enhanced CT. Morbidity and mortality were assessed with particular reference to limb patency and peri-graft flow (endoleak).
Results: All deployments were successful. Exclusion of the aneurysm sac was achieved in 55 patients (86 per cent). There were three deaths (perioperative mortality 4·7 per cent) but no major complications. Of four proximal endoleaks; one sealed spontaneously, one persists and two patients died following attempted open repair. Another patient died from a myocardial infarction on day 3. Of five distal endoleaks, three sealed spontaneously and two required further endovascular intervention. Six grafts have suffered unilateral limb occlusion and CT has identified three late distal endoleaks, each requiring endovascular repair. Three further patients have died (>30 days, two unrelated, one graft infection).
Conclusion: Mid-term results confirm that modular bifurcate ASGs are suitable for the treatment of selected AAAs. The development of late endoleaks is a cause for concern and continued follow-up is required.

Poster 102

Continuous ambulatory venous pressure monitoring in the lower limb

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Background: Conventional study of ambulatory venous pressure (AVP) in the lower limb is a useful diagnostic tool in the management of venous disease and involves monitoring venous pressure while the patient performs standard tiptoe exercises in a laboratory setting. This method is not truly ambulatory as the equipment used is bulky and does not allow the patient to perform normal activities. A method of monitoring continuous AVP which avoids these problems has been developed.
Method: We cannulated the long saphenous vein in seven normal subjects using a blue Venflon. This was attached to a pressure transducer and venous pressure recorded using a Psion II Organiser and appropriate software. The activity of the subjects was assessed using the Numact activity monitor. This consists of two position sensors and an accelerometer connected to a Psion Series 2 Organiser.
Results: The monitoring devices were well tolerated by all subjects who were able to perform their normal activities unrestricted. A total of 47 h of monitoring were carried out. The mean venous pressure was 66 mmHg (range 47–82 mmHg).
Conclusion: This new technique is able to monitor true AVP in subjects during normal activity. This technique should prove valuable as both a research tool and clinical investigation.

Poster 103

Carotid sinus nerve blockade is of no value in carotid endarterectomy

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Background: Intraoperative local anaesthetic (LA) carotid sinus nerve blockade is believed to stabilize arterial blood pressure (BP) during carotid endarterectomy. We investigated the influence of LA and whether BP fell as LA wears off postoperatively in a double-blind controlled trial.
Method: Fifty-nine patients, mean age 69 years (range 53–84 years), were randomized to LA with 5 ml of 0·5 per cent lignocaine or placebo (normal saline) after initial dissection. Patients who had resection of the carotid sinus nerve for bifurcation reconstruction were grouped separately. General anaesthesia was standard with BP and end-tidal carbon dioxide controlled. BP was monitored via an intra-arterial cannula during and for 6 h after surgery and expressed as (i) the mean and (ii) the variability of systolic BP as the mean of standard deviations. Periods of hypotension during the wear-off period were expressed as the percentage of patients who had a fall in systolic BP of ≥20 per cent compared to the intra-operative mean for that patient.
Results:

	Systolic pressure (mmHg)				
Group (*n*)	Pre-operative	Intra-operative	6 h post-operative	Vasoactive drug use	Hypo-tension
Local anaesthetic (21)	153	139 (16·7)	126 (13·4)	81%	57%
Placebo (25)	156	136 (16·6)	132 (13·3)	72%	56%
Resection (13)	157	141 (18·8)	156* (23·0)*	62%	62%

*$P<0{\cdot}001$ analysis of variance.

Conclusion: Excision of the carotid sinus nerve is associated with higher BP in the immediate postoperative period. Lignocaine infiltration of the carotid sinus nerve is of no value in reducing fluctuations in BP during or after carotid endarterectomy.

Poster 104

The influence of carotid disease on cognitive function following coronary artery bypass

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Background: Neurological complications are a leading source of morbidity and mortality following coronary artery bypass grafts (CABG), frequently delaying hospital discharge. The frequency of cognitive dysfunction following CABG was investigated and related to the severity of carotid artery disease.
Method: Duplex Doppler imaging of both carotids was performed preoperatively on 62 patients to seek >70 per cent internal carotid stenoses. A history of symptoms of cerebral ischaemia was recorded. A computerized battery of cognitive function (CF) tests, produced and validated by Cognitive Drug Research Ltd UK, in which patients responded to visual stimuli by pressing a yes/no button in a room free from distractions, were evaluated in terms of reaction time and accuracy. Anaesthesia was standardized with full-flow non-pulsatile cardiopulmonary bypass and 32°C hypothermia. Cognitive function was re-tested at 1 week.
Results: The table shows deterioration in mean CF at 1 week.

	Cerebral symptoms		Right carotid stenosis		Left carotid stenosis	
	Yes (9)	No (53)	>70% (7)	<70% (55)	>70% (4)	<70% (58)
Overall accuracy	0·7	0·2*	0·6	0·3	1·2	0·2**
Overall memory RT	915	147*	1254	151*	2417	109**
Overall RT	1064	267*	1346	280*	2727	220**

Results are all means, *$<0{\cdot}05$, **$P<0{\cdot}0001$, Student's *t*-test, RT = reaction time.

Patients with preoperative symptoms of cerebral ischaemia and/or carotid stenosis >70 per cent, particularly when the dominant hemisphere was involved, were slower and less accurate following CABG.

Conclusion: Although the association between carotid disease and stroke following CABG is well known, the effect on cognitive function is less well documented. Carotid disease clearly relates to cognitive dysfunction following CABG.

Poster 105

First year results of a community based leg ulcer service

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Background: Previous reports of the high success rate of compression bandaging of venous leg ulceration have come mainly from hospital-based specialized clinics. More widespread application of the technique has been disappointing in many centres. The aim of this study was to determine whether a completely community-based leg ulcer service could achieve results comparable to a hospital-based service.
Method: All newly referred patients with leg ulceration over 12 months (01.10.95–30.09.96) were studied prospectively. Each patient in the community-based ulcer clinic was assessed by a specialist vascular nurse with continuous wave Doppler and a proforma detailing aspects of the history and the examination. Sixty-nine patients were referred directly by the general practitioner, of which 54 were suitable for leg compression. A total of 54 patients with 63 ulcerated legs were therefore analysed. All patients assessed had an active leg ulcer for more than 3 months.
Results: Forty-nine limbs were healed within 12 weeks (78 per cent) and 59 limbs were healed within 16 weeks (93 per cent). Four limbs failed to heal during the study (7 per cent). At the end of the study, recurrent ulceration was witnessed in four limbs (7 per cent). The total failure rate at 1 year was eight (13 per cent).
Conclusion: With relevant training, appropriate patient selection and the correct use of four-layer bandaging, high levels of leg ulcer healing can be achieved in an entirely community-based ulcer service without the input of a vascular surgeon.

Poster 106

What were you doing when your graft blocked?

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Background: Circumstances surrounding arterial graft thrombosis are often unknown. A study was undertaken to determine whether late graft occlusion could be associated with specific events or activities.
Method: Patients presenting with a graft occlusion between January 1995 and October 1996 completed a questionnaire requesting details of smoking, diabetes, and mobility. Patients were asked to recall any activity/event that they felt was implicated in graft failure. Hospital notes and vascular laboratory records were consulted to determine peri- and postoperative details.
Results: Forty-eight patients (35 men; 13 women) responded. Median (range) age was 68 (46–91) years. Median time to occlusion was 6 (1–108) months. Indications for reconstruction were critical ischaemia (34); severe claudication (14). Twenty-seven of 48 (56 per cent) patients admitted to continued smoking; 3/48 (6 per cent) were diabetic. At time of occlusion 44/48 (92 per cent) were mobile. Twenty-five of 48 (52 per cent) patients correlated graft failure with an activity/event. Of these, 15/16 patients with a failed PTFE BK femoropopliteal graft equated failure with a specific situation ($P<0{\cdot}0001$, Fishers exact test). Prolonged knee flexion (kneeling (4); sitting (5); travel: car (4), rail (1), aircraft (1) was related to failure of 15/25 grafts. In four patients grafts occluded whilst asleep. Dehydration was implicated in five cases: pancreatitis (1); gastro-enteritis (1); renal dialysis (1); inadequate fluid intake (+alcohol) in hot climate (2). One aortobifemoral limb thrombosed on ceasing warfarin therapy.
Conclusion: Patients' perceptions of causes of graft thrombosis are a salutory reminder of potential problems. Warning patients of the risks of dehydration, ensuring scrupulous routing of grafts across the knee, and avoidance of prosthetics where possible, are messages that must be reinforced.

Poster 107

Variability in measurement of internal carotid stenosis by arch angiography and duplex ultrasonography

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Background: The aims were: first, to determine inter- and intra-observer variability in measuring internal carotid artery (ICA) stenosis by arch angiography, using the techniques employed by the North American (NASCET) and European (ECST) symptomatic carotid surgery trials; second, to compare arch angiography with duplex ultrasound in the measurement of ICA stenosis.
Method: Three observers graded ICA stenoses bilaterally on 50 consecutive arch angiograms performed for symptomatic carotid disease using both NASCET and ECST criteria. The same patients also had duplex assessment of their ICA stenoses.
Results: Inter-observer agreement on arch angiography was moderate to good and was closer with NASCET (kappa 0·69, 0·77, 0·66) than with ECST (kappa 0·66, 0·62, 0·58). Intra-observer agreement between NASCET and ECST was poor (95 per cent agreement limits: −24 per cent to +28 per cent, ECST minus NASCET bias +1·93 per cent, Bland-Altman) and decreased with decreasing observer experience. For the best observer this gave a 5 per cent operative misclassification rate (95 per cent C.I., 2 per cent–11 per cent). Agreement between duplex and both angiographic techniques was worse (NASCET 95 per cent agreement limits: −16 per cent to +36 per cent, duplex minus NASCET bias +10 per cent; ECST 95 per cent agreement limits: −18 per cent to +32 per cent, duplex minus ECST bias +7 per cent, Bland-Altman) with a higher operative misclassification rate (21 per cent NASCET, 19 per cent ECST).
Conclusion: Variability is significant between NASCET and ECST measurements of ICA stenoses on arch angiography, but NASCET gives the more consistent results between different observers. Agreement between duplex and arch angiography (ECST or NASCET) is poor and is of considerable clinical significance.

Poster 108

Gender differences in abdominal aortic aneurysm repair

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Background: North American data have shown that female gender adversely affects selection for, and mortality from, abdominal aortic aneurysm (AAA) repair. The aim of this study was to examine whether such differences can be demonstrated in patients managed in a UK regional vascular unit.
Method: Analysis of a prospectively gathered database of 1515 patients operated for asymptomatic (n = 492), symptomatic (n = 350) and ruptured AAA (n = 673) and 139 patients who were not operated for ruptured AAA between 1 January 1976 and 31 December 1996.
Results: The male:female ratio for patients undergoing repair of asymptomatic, symptomatic and ruptured AAA was 4·8, 4·0 and 5·7:1, respectively. There was no significant difference between women and men with regard to mortality after asymptomatic (8 of 103, 8 per cent vs 22 of 389, 6 per cent, P = 0·49, Fisher's exact test), symptomatic (9 of 87, 10 per cent vs 24 of 263, 9 per cent, P = 0·83, Fisher's exact test) and ruptured AAA repair (48 of 119, 40 per cent vs 200 of 554, 36 per cent, P = 0·8,

χ^2 test). A significantly higher proportion of women admitted with rupture were not operated (54 of 173, 31 per cent vs 85 of 639, 13 per cent, $P <$ 0·001, χ^2 test) such that the overall mortality rate for rupture was significantly higher in women than in men (102 of 173, 59 per cent vs 285 of 639, 45 per cent, $P <$ 0·001, χ^2). There was no significant difference in age between women (median 74, range 51–85, years) and men (median 71, range 43–86, years) operated for rupture, or between women (median 81, range 63–93, years) and men (median 82, range 63–93, years) with rupture who were not operated.
Conclusion: These data do not support the contention that female gender adversely affects the operative mortality associated with elective or emergency repair of intact or ruptured AAA. However, fewer female patients with rupture were operated and consequently overall survival was reduced.

Poster 109

Ruptured aortic aneurysm: the decision not to operate

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Background: Some patients with a ruptured abdominal aortic aneurysm (RAAA) do not undergo surgery because their prospects of survival and quality of life are so poor. The decision not to operate is often difficult. This study examined the criteria used by vascular surgeons in deciding against operation for RAAA.
Method: A questionnaire was sent to all 404 members of the Vascular Surgical Society about the organization of services for patients with RAAA, and about factors that might influence their decision against operation (no influence; may influence; seldom operate; never operate).
Results: The response rate was 81 per cent (323 replies) of whom 97 per cent practiced some case selection. Age >80 influenced 77 per cent, and 54 per cent seldom or never operated on patients >85. Of the other criteria, the single most influential factor was severe neurological disease (75 per cent seldom or never operate), while cardiac, pulmonary and renal disease influenced 22 per cent, 28 per cent and 21 per cent, respectively to operate seldom or never (74 per cent if two or more of these). Other factors that had some influence for most surgeons were cardiac arrest (85 per cent), loss of consciousness (74 per cent), prolonged hypotension (73 per cent), and long-term nursing care (87 per cent). By contrast, factors that influenced few surgeons were haemoglobin <9 g/dl (30 per cent) and absence of a close relative (33 per cent). Possible medicolegal consequences of not operating influenced only 22 per cent. If the situation becomes hopeless during the operation then 85 per cent of surgeons terminate the procedure at that stage.
Conclusion: Case selection for RAAA surgery will remain difficult, but these data help to inform the debate.

Poster 110

Is photoplethysmography useful in predicting the improvement in venous function after surgery for chronically ulcerated limbs?

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Background: This study aimed to assess the role of preoperative digital-photoplethysmography (d-PPG) in predicting postoperative venous function, and therefore potential benefit of surgery, in chronic leg ulcer patients.
Method: Patients were assessed in a one-stop vascular clinic, including ankle:brachial pressure index and colour venous duplex imaging. Patients with ulcerated limbs and superficial reflux alone were offered surgery and assessed by d-PPG. Venous refill time (VRT) was measured preoperatively, with and without below-knee tourniquet (BKT), and repeated after surgery.
Results: Twenty-four limbs underwent superficial venous surgery with pre- and postoperative measurements. Median (inter-quartile range) preoperative VRT increased from 12 s (8–18·5) to 26 s (20–31·5) with tourniquet ($P<0·01$) and to 19·5 s (13·5–22) after surgery ($P<0·01$, Wilcoxon signed rank). The percentage increase in VRT with tourniquet correlated with the percentage increase after surgery ($r = 0·528$, $P = 0·01$, Spearman's rank). Median refill times for healed ($n = 19$) and non-healed ($n = 4$) limbs by 12 weeks postoperatively were as follows:

	VRT preoperative	VRT with BKT	VRT postoperative
Healed ($n = 19$)	10·7	26	21
Non-healed ($n = 4$)	12·5	23·5	13

Conclusion: PPG predicts improvement in venous function after surgery in chronic ulcerated limbs with superficial reflux alone. This may improve patient selection for surgery and predict clinical outcome.

Poster 111

What happens to patients enrolled into an exercise programme?

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Background: This study aimed to investigate the rate of re-referral and continuing involvement for claudicants enrolled into an exercise training programme.
Method: Records were reviewed of 108 patients with intermittent claudication enrolled into an exercise programme, and followed up at 3, 6 and 12 months.
Results: Fifty-seven (53%) patients remained in the programme and under follow-up at 1 year. Of the 51 patients falling out of the programme, only eight (7 per cent) were re-referred for further surgical evaluation; five underwent angioplasty, and three had surgery. Fifteen patients (14 per cent) were discharged from the programme, 12 (11 per cent) failed to attend for follow-up, 11 (10 per cent) withdrew due to failing health, three (3 per cent) for miscellaneous reasons, and two (2 per cent) died. Patients were more likely to be discharged or withdraw (excluding death or re-referral) if they were involved in a home exercise programme ($n = 30$) compared to an exercise class ($n = 11$; $P = 0·0001$ χ^2).
Conclusion: Eighty-four per cent of patients withdrew or were discharged from the exercise programme for reasons unrelated to the need for surgical or radiological intervention. Exercise training is an effective treatment and does not merely delay the time to invasive intervention.

Poster 112

Who benefits most from an exercise training programme?

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Background: This study aimed to investigate which patients gain the greatest improvement in walking performance from a supervised exercise programme.
Method: Sixty-eight patients (median age 66 years, range 33–90) enrolled into an exercise programme, and were evaluated at 3, 6 and 12 months by treadmill assessment of walking performance.
Results: Overall median maximum walking distance (MWD) improved from an initial level of 98 m to 267 m at 3 months, 357 m at 6 months and 730 m at one year ($P = 0·0001$ Kruskal–Wallis ANOVA). Patients with disease confined to the superficial femoral/popliteal segment ($n = 39$) showed a greater benefit from exercise training than those with aorto-iliac disease ($n = 29$). The respective median MWD at 3 months were 371 m vs 126 m ($P = 0·009$ Mann–Whitney, at 6 months were 618 m vs 144 m ($P = 0·009$

Mann–Whitney), and at 12 months 1000 m vs 288 m ($P = 0{\cdot}07$ Mann–Whitney). Patients walked significantly further if they attended a supervised exercise class ($n = 24$) rather than being enrolled into a home exercise programme ($n = 44$), and if they recorded an initial MWD of greater than 100 m. Twenty-eight patients, who had received previous surgery or angioplasty, still improved their MWD significantly from the initial level.

Conclusion: These data suggest that patients with disease confined to the superficial femoral/popliteal segment, who have not had previous intervention, who attend a supervised exercise class, and with an initial MWD of greater than 100 m, will gain greatest benefit from exercise training.

Poster 113

The influence of systemic factors and pre-existing venous intimal hyperplasia in the detection of 'at risk' infra-inguinal vein grafts

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Background: The relevance of elevated plasma lipoprotein (a), fibrinogen, and homocysteine levels, and the presence of pre-existing venous intimal hyperplasia (IH) to the development of vein graft stenosis (VGS) have been disputed. This study aimed to investigate the association between these plasma factors, IH and outcome, and the value of these in selecting grafts at high risk of failure.

Method: Lipoprotein (a), fibrinogen and homocysteine were measured in each patient and a vein biopsy taken. Pre-existing IH was graded semi-quantitatively (0 = no IH, I = mild, II = moderate, III = severe). Patients underwent duplex graft surveillance.

Results: Sixty-three grafts in 56 patients were recruited. Forty-seven were available for follow-up (mean 15, range 5–30 months). Patients with no pre-existing IH had significantly lower homocysteine levels than those with IH ($n = 50$, $P = 0{\cdot}007$ Mann–Whitney test), but significantly higher lipoprotein (a) levels ($n = 50$, $P = 0{\cdot}012$ Mann– Whitney test). Twenty-four of the 47 grafts developed VGS. There was no association between VGS and age, sex, diabetes, or level of reconstruction. Mean plasma fibrinogen was higher, though not significantly, in those with VGS (4·16 vs 3·18 g/l, $n = 45$, $P = 0{\cdot}09$ Mann–Whitney test). Grafts with grade II/III IH were significantly more likely to stenose than those with grade 0/I ($n = 40$, $P < 0{\cdot}025$ χ^2 test). There was a highly significant association between patients with grade II/III IH and/or raised fibrinogen and VGS ($n = 38$, $P < 0{\cdot}005$ χ^2 test).

Conclusion: Plasma homocysteine levels correlated with the presence of pre-existing IH, which itself correlated with VGS. There is a marked relationship between the presence of raised plasma fibrinogen levels and pre-existing IH with the development of VGS, and these investigations may allow early identification of grafts requiring intense surveillance.

Poster 114

Endothelial dysfunction and cold pressor vasoactivity in young cigarette smokers

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Background: Cold pressor vasoactivity, which is thought to depend in part on endothelial vasodilator function and also on adrenergic stimulation, was assessed in young smokers. The effects of Taurine supplementation, which we previously found to restore endothelial function, was investigated in this group.

Method: We studied five healthy smokers with a self-reported smoking history of 2-pack years and five control non-smoking subjects. Using a 7 MHz linear array ultrasound transducer, we measured brachial artery diameter in the right arm at baseline and during and after left hand immersion in ice water for 3 min. Measurements were taken during and after the cold pressor stimulus at 1-min intervals up to 10 min post-immersion. On a separate occasion a haemodynamic evaluation as performed at baseline and 1 and 3 min post-immersion of the opposite hand in ice. Cold pressor response was then re-assessed in Taurine (1·5 g/day/5 days) treated smokers.

Results: Cold pressor-induced vasodilatation was present at 1 min in controls, in contrast to smokers in whom the cold pressor stimulus induced vasoconstriction at this time point ($P = 0{\cdot}02$). After supplementation with Taurine the cold pressor-induced vasoconstriction in smokers was reduced ($P = 0{\cdot}05$). After treatment with Taurine ($n = 3$), cold pressor-induced vasoconstriction was reduced in the smokers, but vasoactivity was not restored to that of controls.

Cold pressor effect: changes in vessel diameter.

Smokers	Non-smokers	Smokers treated with Taurine
4·04% ± 1·34% Constriction	4·22% ± 5·04% Dilatation	0·5% ± 1·9% Constriction

Conclusion: These data confirm the presence of endothelial dependent and independent abnormal vasoactivity in otherwise healthy young smokers, abnormalities which may have an adverse impact on vascular reconstruction. The failure to reverse this completely with Taurine underscores the need to stop cigarette smoking.

Poster 115

Day-case varicose vein surgery is feasible for the majority of patients and has a low recurrence rate

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Background: While day-case surgery has become standard practice for many general surgical procedures, patients are still admitted overnight for varicose vein surgery in the majority of centres. The feasibility and results of large-scale day-case varicose vein surgery were examined in this study.

Method: All patients presenting with varicose veins to a single surgeon from 1989 to 1997 were considered for day-case surgery. Patients were included on the basis of anaesthetic suitability, adequate social support and living within 50 km of the hospital. Preoperative duplex scanning was performed routinely. Patients were scheduled for follow-up at 4 weeks and were contacted for a telephone questionnaire in September 1997.

Results: In this interval, 900 day-case procedures have been carried out on 686 patients. The mean age was 45 years (range 17–61) and the male:female ratio was 1:4. Surgery was performed for recurrent veins in 5·4 per cent. Operative procedures performed included saphenofemoral ligation with stripping of the long saphenous vein and avulsions (81·9 per cent), sapheno-popliteal ligation with avulsions (5 per cent), combined saphenofemoral and -popliteal ligation (7·7 per cent) and avulsions alone (5·4 per cent). Overnight admission was required in 27 cases (3·5 per cent). The commonest reason for admission was postoperative nausea and vomiting ($n = 11$). There were no major complications of surgery. Attendance at follow-up clinics was 92 per cent. The principal complications included pain (3·3 per cent), haematoma (1·7 per cent) and numbness (1·3 per cent). 95·6 per cent of patients were discharged after one visit. Four hundred and forty-five patients (64 per cent) were contacted by phone. Average follow-up was at 32 months (range 13–74 months). There was a reported 9 per cent recurrence rate and these patients have been offered further follow-up. More than 90 per cent expressed general satisfaction with the day-case approach and the results of surgery.

Conclusion: Day-case varicose vein surgery is feasible on a large scale, with minimal morbidity, few overnight admissions and a low recurrence rate. It could prove a useful way to reduce the long waiting lists for varicose vein surgery which exist in many hospitals.

Poster 116

Degree of internal carotid artery stenosis and plaque morphology do not influence embolization

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Background: This study aimed to determine whether the degree of internal carotid artery (ICA) stenosis as observed by transcranial doppler (TCD) insonation of the middle cerebral artery (MCA) and plaque morphology determined by duplex were related to the propensity of a lesion to embolize.

Method: Thirty-nine patients undergoing carotid endarterectomy underwent TCD of their MCA for 30 min 2 days before surgery and all embolic signals were recorded. The degree of ipsilateral carotid stenosis and Gray Weale (GW) plaque classification were assessed by duplex preoperatively. During intraoperative MCA velocity monitoring any embolization prior to ICA clamping was recorded.

Results: Twenty patients had a stenosis between 70 per cent and 89 per cent, and 19 of 90 per cent and over. There was no difference in the two groups in terms of preoperative emboli ($P = 0{\cdot}12$), intraoperative preclamp emboli ($P = 0{\cdot}32$) or any emboli ($P = 0{\cdot}43$). The mean degree of stenosis for the non-embolic group was 87·3 per cent and for the embolic group 88·3 per cent. There was also no difference in the fall in MCA blood velocity on clamping between patients with emboli, and those without ($P = 0{\cdot}51$). There was no difference between the embolic and non-embolic group in terms of the GW classification of the plaque ($P = 0{\cdot}81$).

Conclusion: The degree of stenosis of the ICA and plaque morphology did not influence observed embolization.

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Leading articles

Venous insufficiency and perforating veins

Perforating veins perform a normal function in transporting superficial venous blood inward to the deep system for further transit to the heart. However, in the presence of superficial reflux, normally functioning perforating veins can produce a deleterious effect on the deep venous system, causing elongation and dilatation of major deep veins and subsequent valvular insufficiency. This impairs venous function. Perforating veins may also demonstrate abnormal outward flow which may well be associated with the cutaneous changes of severe chronic venous insufficiency. In this way, perforating veins are deleterious to the health of medial ankle skin.

Deep vein reflux accompanies saphenous vein reflux in 20 per cent of limbs with varicose veins and in the apparently normal contralateral limb in 3·5 per cent[1]. This retrograde circuit was described by Trendelenburg. The usual starting point for reflux is the saphenofemoral junction but actually the reflux may develop from any proximal incompetent perforating vein such as the mid-thigh Hunterian or the anteromedial Boyd. The endpoint of this reflux is where the majority of the reflux flow re-enters the deep circulation. Treatment of this form of reflux consists of removing the superficial limb of the reflux circuit. This results in haemodynamic improvement as assessed by duplex ultrasonography[2]. In 29 limbs that demonstrated preoperative superficial femoral deep venous reflux in association with superficial reflux in the greater saphenous system, 27 were found to have total abolition of the deep venous reflux after groin-to-knee saphenous stripping. This initial report was confirmed later by Sales *et al.*[3] who described 17 limbs with reflux in the femoral deep venous system in addition to superficial reflux. All of these patients had removal of the proximal greater saphenous vein in concert with multiple stab avulsions of identified varicosities. Postoperative investigation revealed that 16 of the 17 limbs had complete resolution of the femoral reflux.

In a study of the mechanisms by which haemodynamic function improves following long saphenous surgery, Hammarsten's group[4] preserved the greater saphenous vein by flush ligation and division of the greater saphenous vein at the saphenofemoral junction, followed by interruption of the perforating veins which were detected by preoperative phlebography. These were ligated flush at the deep fascia through 2–3-cm incisions. Frequently, the skin incision was extended and the perforating vein ligated subfascially. The preoperative diameter of the long saphenous vein was reduced by 40 per cent at four different levels in the operated legs. The photoplethysmographic venous return time increased by 2·4 times above baseline and the decrease of the greater saphenous vein diameter correlated with the increase in venous refill time. So eliminating gravitational reflux by proximal saphenous vein ligation and decreasing the retrograde flow through normally functioning perforating veins by ablation of these perforating veins improved venous function and allowed the saphenous vein to decrease in diameter.

Hach[5] studied limbs by phlebography and determined that at the femoropopliteal junction the normal deep venous diameter in 75 limbs was 12 mm. However, in limbs with superficial reflux from groin to ankle, the diameter of the femoropopliteal junction increased to 17 mm. Furthermore, elongation of the vein was seen. The normal angle of the femoropopliteal junction was 158°, nearly straight; this changed to 142°, a significant angulation. An enormous popliteal vein tortuosity was also clearly seen on phlebography. Hach postulated that the calf muscle pump became overloaded because of the reflux through the greater saphenous vein re-entering perforating veins.

As some surgeons relate outward flow in perforating veins to severe skin changes of venous insufficiency, interruption of calf perforating veins by endoscopic techniques has been an attractive concept. The technique was explored early on in German-language countries where it has even been applied in the interruption of perforating veins during treatment of primary varicose veins. In that situation, it is not clear whether perforating vein interruption contributes much to the operation. In fact, the benefit of sectioning perforating veins even in limbs with chronic venous insufficiency remains unproven by controlled data. This is true even though the beneficial effects of perforator interruption are quite obvious clinically. The deleterious nature of calf perforating vein outward flow has been confirmed by endoscopic halting of outflow by subfascial perforator vein interruption. DePalma and Kowallek[6] showed in a crossover study that failure of conservative care could be reversed by intervention with sectioning of perforating veins.

Preliminary investigations by the author and his colleagues have proved the safety and efficacy of endoscopic perforator interruption and have now been extended. The single-port open-scope approach is still used. In studying patients with various grades of venous insufficiency, it was found that larger perforators are associated with more severe venous insufficiency and these are greater in number than in patients with simple varicose veins[7]. It was observed that wound healing in patients with an open ulcer is accelerated by the operative intervention[8]. The preliminary report by Gloviczki *et al.*[9] on the subject described 11 limbs in nine patients operated on by the multiple-port system and gas insufflation. In seven limbs there was improvement of ulcer healing. In three limbs the ulcer failed to heal, and in one limb the ulceration was not improved by the intervention.

In the subfascial endoscopic perforator surgery report from the North American Registry, there were preliminary data on 148 patients who had the operation in 17 institutions in 3 years after 1993[10]. Seventy per cent of the patients treated had active ulcers and 15 per cent had healed venous ulcers. The clinical score, which was a measure of morbidity due to the venous insufficiency, improved markedly from the preoperative state. During a very short mean follow-up of only 5·4 months, the venous ulcers had healed in 88 per cent of those with an active ulcer at the time of the operation.

Although it is acknowledged that normal perforating vein function assists in returning lower extremity blood to the central circulation and the heart, it appears that in pathological states the perforators are doubly deleterious. When superficial reflux is present, their normal function serves to overload and stretch the deep veins. When their check valve function fails, they are frequently associated with the severe cutaneous changes of severe chronic venous insufficiency.

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Surgical treatment of anal incontinence

Anal continence is the ability both to retain faeces and to expel faeces at a proper place and at a proper time. Continence is not simply a retention mechanism, it is also the ability to defaecate in a normal way. Of the various factors that contribute to continence, the anal sphincter and pelvic floor are but two[1]. While the various surgical treatments for incontinence focus mainly on sphincter function, when it is the consistency of faeces, hyperperistalsis of the bowel, lack of compliance of the rectum or lack of sensation that are the main causes of incontinence, any operation aimed simply at restoring sphincter function will be unlikely to result in improvement. It is clear that a good clinical history and physical examination, with anorectal laboratory assessment, are essential to determine the extent to which dysfunction of the sphincter and pelvic floor contribute to the problem.

In the past most surgeons considered only the first part of the definition of continence and tried to fashion a closing mechanism. This led to the creation of a rigid narrowing of the anal canal. Examples of such surgery are the Thiersch wire and fascia lata plasty. These rigid constructions introduced an obstruction and patients were left with enormous difficulty with defaecation. Although they did not lose stool, the almost unsolvable problem of severe constipation was hardly an improvement in quality of life. Apart from the complication of obstruction, erosion of the wire or tendinous tissue through the anal canal was a frequent occurrence. Infection and pain often led to the need for a colostomy. Although in some older publications reasonable results were described in terms of restoration of continence, it is not clear whether this meant no loss of stool or restoration of controlled defaecation. None of these publications mention anything about outlet obstruction.

A more logical approach is to restore continuity to damaged sphincters[2]. The direct end-to-end suturing or the overlapping Parks anal repair gives the patient an intact circular sphincter that can close and dilate, provided that the neurogenic pathways are intact. The overall results of such an approach are quite good and much more satisfactory than those of the rigid reconstructions. Most patients develop a restoration of the anorectal inhibitory reflex, indicating an intact neurogenic input.

The pelvic floor is also considered an essential factor in anal continence. Many elderly women with incontinence have a weak puborectal sling; electromyography of the pelvic muscles shows signs of denervation and defaecography demonstrates a disappearance of the anorectal angle. Parks described the method of postanal repair to remedy this situation and, while it did, indeed, strengthen the posterior aspect of the anus with good results initially, the effect disappeared over time in most patients[2]. This is not surprising as the process of denervation is not hindered and eventually the restored anorectal angle widens. Preanal suturing of the puborectal sling, usually in combination with anal repair, gives better results.

When all treatments aimed at directly restoring sphincter or pelvic floor function fail or are contraindicated, one can consider trying to provide this function by using another muscle or an artificial sphincter. The gracilis and the gluteus are the most commonly used muscles. The latter has the advantage of being a more tonic muscle that already has an auxiliary role in 'emergency' situations; brain coordination makes it to some extent attractive to use part of the gluteus as a sphincter replacement. However, the operation is complex and it requires both gluteal muscles to encircle the anal canal[3]. Furthermore, active contraction is only possible through brain activity. The gracilis muscle is easier to free and it is technically easier to bring it around the anus. Its use has hardly any effect on leg function. The muscle is, however, fatiguable with a vast majority of type 2 fatiguable fibres. It is a voluntary muscle which can only be contracted when the patient really concentrates. However, stimulation of the transposed muscle with the help of an implanted electrical stimulator allows a change in the muscle composition towards infatiguable type 1 fibres and the muscle contracts automatically on the electrical pulses[4]. With the addition of electrical stimulation the initially unsuitable graciloplasty is transformed into an automatic non-fatiguable contractor of the anus. The stimulator can be switched on and off by remote control and in this way normal defaecation can be mimicked[4,5]. Stimulation of the gluteus needs higher voltages; the results are not as good as those of dynamic graciloplasty (which are very promising).

Implantation of the artificial inflatable sphincter has almost the same indication as graciloplasty, and with similar results. The initial fear of severe perianal infection appears unfounded[6,7]. An inflatable cuff is placed around the anus and is operated by squeezing a pump located in the scrotum or labia.

The use of sacral nerve stimulation is still experimental. It was developed to treat urinary incontinence but an influence on the anorectum was noted as a side-effect[8]. This new technique, like those outlined above, requires significant further evaluation before it will be possible to make a definite statement about indications. As always, the longer term results will be a major factor.

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Review

Cytogenetics and the surgeon: an invaluable tool in diagnosis, prognosis and counselling of patients with solid tumours

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Background Cytogenetic studies have become an important part of tumour characterization. In a minority of tumours cytogenetic and/or molecular studies may be of help for diagnosis, selection of treatment protocols and predicting outcome.

Methods This article reviews the literature on solid tumour translocations and established family cancer syndromes. In addition, the potential importance of genetics in management of patients with breast, ovarian and pancreatic carcinoma is reviewed.

Results and conclusion Cytogenetic analysis of tumours may help confirm the diagnosis when conventional histology demonstrates no evidence of differentiation along a particular tissue pathway. For patients with well defined cancer syndromes, cytogenetic and molecular analysis offers the prospect of screening to reduce the risk of malignant disease. For many malignancies the underlying genetic anomalies are gradually being elucidated. Further studies designed to demonstrate the significance of these findings can only be undertaken if tumour material is collected and stored in optimal conditions for cytogenetic and/or molecular biological studies.

The past two decades have seen an exponential increase in our understanding of the human genome. Genetic studies in human neoplasms have not only shed light on the events leading to the development of tumours but have also suggested new methods for diagnosis, prevention and treatment of malignant disease.

Genetic alterations may be studied at different levels. Changes in the amount of DNA within tumour cells can be detected using flow cytometry or absorption photocytometry. Aneuploidy (chromosome number other than the normal diploid 46 chromosomes) has been associated with poor prognosis in a number of neoplasms, including colorectal cancer, melanoma, node-negative breast cancer, pancreatic carcinoma, neuroblastoma and acute lymphoblastic lymphoma[1–11]. Changes in ploidy are, however, only a gross measurement of overall loss or gain of DNA.

Classical cytogenetic techniques require suspensions of living cells which are capable of mitosis. If colchicine is added, cell division is arrested in metaphase when the chromosomes have replicated and separated. Metaphase spreads are obtained by lysing the cells and staining gives a unique pattern of labelling for each chromosome. This technique demonstrates the number of chromosomes present within a cell and allows detection of translocations. Fluorescence *in situ* hybridization (FISH) makes use of fluorescence-labelled DNA probes which bind in a highly specific fashion to complementary DNA sequences, allowing demonstration of structural chromosomal abnormalities in non-dividing cells.

Identification of the products of translocations or specific gene mutations requires molecular techniques. The polymerase chain reaction (PCR) allows amplification of specific regions of DNA provided that the target gene is known[12]. This technique allows identification of single nucleotide mutations. Reverse transcriptase–PCR (RT–PCR) allows amplification of messenger RNA, enabling detection of the fusion products of chromosomal translocations or tumour-specific proteins.

Chromosomal analysis of human cancer cells has demonstrated a large number of chromosomal abnormalities clustered within specific areas of the genome[13]. Although many of the tumours with consistent identifiable cytogenetic abnormalities are uncommon, they are likely to present primarily to non-specialist centres (*Tables 1* and *2*)[14–16]. The general surgeon should be aware of recent advances in tumour biology, as this has implications for the handling of surgical specimens and further management of the patient. Traditional fixation of surgical specimens in formalin followed by paraffin embedding affords excellent preservation of tissue allowing, in most instances, a clear histological diagnosis to be made following light microscopy. However, many techniques of genetic analysis cannot normally be performed on formalin-fixed tissue.

Cytogenetics and tumour classification: lymphoma subtypes

Non-Hodgkin's lymphoma (NHL) in adults has been subject to a number of different pathological classifications[17,18]. The importance of cytogenetics in differentiating the various forms of lymphoma has been documented over the past two decades. In addition, cytogenetic analysis has made an important contribution to our understanding of the pathogenesis of malignant lymphoma, and has led to the discovery of many important genes involved in cell cycle control and apoptosis.

Many of the cytogenetic abnormalities observed in NHL involve the genes encoding antigen receptors of B and T lymphocytes. These undergo rearrangement during

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lymphocyte differentiation. Many of the cytogenetic abnormalities observed are translocations involving the immunoglobulin (Ig) heavy-chain region (IgH at 14q32) and, less commonly, the kappa and lambda light-chain gene locus (at 2p12 and 22q11 respectively) in B-cell NHL; the T-cell receptor gene loci (alpha at 14q11, beta at 7q35, gamma at 7p11 and delta at 14q11) are involved in T-cell NHL[19–22].

The translocation partners of the antigen receptor genes often involve genes that have fundamental roles in cellular physiology. For example, the t(8;14)(q24;q32) seen in Burkitt's lymphoma translocates the c-*myc* gene, which is important in the control of cellular proliferation, into the IgH gene locus and leads to c-*myc* overexpression. Abnormalities of the c-*myc* gene locus are almost universal in Burkitt's lymphoma, whether involving the classical t(8;14)(q24;q32) (seen in 80 per cent of Burkitt's lymphomas) or the kappa and lambda light-chain gene loci, and are thus important in the definition of the disease[23]. Other important genes involved in translocations with immunoglobulin gene loci include *bcl-2* at 18q21 in follicular lymphoma[24–26], cyclin D at 11q13 in mantle cell lymphoma[27–31] and 3q27 (which encodes a zinc finger protein termed bcl-6) in *de novo* diffuse large B-cell lymphoma[32–35].

In some subtypes of NHL chromosomal translocations occur which do not involve antigen receptor genes but other constitutionally expressed genes, such as the nucleophosphomin gene in the t(2;5)(p23;q35) seen in anaplastic large cell lymphoma of T/Null lineage. This

Table 1 Syndromes in which gene abnormalities are known to predispose to tumour development

Syndrome	Neoplasm	Gene	Chromosome	Reference
Multiple endocrine neoplasia type 2	Medullary thyroid cancer Parathyroid adenoma/hyperplasia Phaeochromocytoma	*RET*	10	88
Familial breast and ovarian cancers	Breast and ovarian carcinomas	*BRCA1* and *BRCA2*	17 13	94–96 97, 98
Familial adenomatous polyposis	Colorectal adenoma/carcinoma Adenoma of gastric antrum, duodenum, periampullary region and terminal ileum	*APC*	5	99–101
Gardner's syndrome	Colorectal, thyroid, adrenal, biliary and liver malignancies Desmoid tumours	*APC*	5	99
Turcot's syndrome	Colorectal cancer Malignant brain tumours	*APC*	5	99
Hereditary non-polypopsis colorectal cancer	Colorectal cancer Ovarian cancer Endometrial carcinoma	*hMSH2* *hMLH1* *hPMS1* *hPMS2*	2p 3 2q 7	73, 74 75 76 76
Li-Fraumeni syndrome	Breast cancer Sarcomas Adrenal cortical carcinoma	*TP53**	17	106
Familial melanoma	Melanoma Pancreatic carcinoma	*p16*†	9	71, 77, 78
Multiple endocrine neoplasia type 1	Parathyroid adenoma/hyperplasia Pancreatic islet cell tumours Anterior pituitary adenoma Adrenal cortical adenomas Carcinoid tumours	—‡	11	107
Neurofibromatosis type 1	Schwannomas Sarcomas Gliomas	*NF-1*	17	105
Neurofibromatosis type 2	Acoustic schwannomas Meningiomas Gliomas	?merlin§	22	108, 109
von Hippel-Lindau disease	Basal cell carcinomas Haemangioblastomas	*VHL*	3p	110, 111
Familial retinoblastoma	Retinoblastoma Osteosarcoma Rhabdomyosarcoma	*RB*	13	112
WAGR**	Wilms' tumour	*WT1*††	11p13	113
Beckwith-Wiedemann syndrome	Wilms' tumour Adrenocortical cancer Hepatoblastoma Rhabdomyosarcoma Neuroblastoma	—‡	11p15	113, 114
Gorlin's basal cell nevus syndrome	Basal cell carcinomas Phaechromocytoma	*PTC*	9	104
Hereditary pancreatic cancer/ hereditary pancreatitis	Pancreatic carcinoma	*DPC-1* and *DPC-4*	13 18	115, 116 117

*also known as *p53*; †also known as *MTS1*, *p16*^{ink4} and *CDKN2*; ‡gene not identified at present time; §candidate gene identified in a small number of neurofibromatosis 2 kindreds; **syndrome consisting *inter alia* of Wilms' tumour, aniridia, genitourinary abnormalities and mental retardation; ††Wilms' tumour gene. DPC, deleted in pancreatic cancer

Table 2 Solid tumours known to be characterized by specific chromosomal abnormalities

Tumour	Genetic anomaly	Fusion transcript	Frequency (%)	Reference
Ewing's sarcoma, pPNET, Askin	t(11;22)(q24;q12)	EWS-FLI-1		42, 43 44, 45
family of tumours	t(21;22)(q12;q12)	EWS-ERG	>95	
	t(7;22)(p22;q12)	EWS-ETVI		46
Desmoplastic round cell tumour	t(11;22)(p13;q12)	EWS-WT1	?	49
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	PAX3-FKHR	80	52
	t(1;13)(p36;q14)	PAX7-FKHR	10–20	57
Synovial cell sarcoma	t(X;18)(p11;q11)	SYT-SSX1 SYT-SSX2	95	118, 119
Clear cell sarcoma*	t(12;22)(q13;q12)	EWS-AFT1	90	120, 121
Myxoid chrondrosarcoma	t(9;22)(q22;q12)		50	122, 123
Endometrial stromal sarcoma	t(7;17)(p15–21;q12–21)		50	124, 125
Myxoid liposarcoma	t(12;16)(q13;p11)	TLS/FUS-CHOP	75	126–128
Well differentiated liposarcoma	Ring and giant chromosomes		80	129
Pleiomorphic liposarcoma	Complex karyotype		90	129
Dermatofibrosarcoma protruberans	t(17;22)(q22;q13)		?	130
Desmoid tumours	Telomeric fusion; d 5(q12–31)		38	131

*Also known as malignant melanoma of soft parts. Identification of this cytogenetic abnormality will help differentiate these tumours from metastatic melanoma. t, translocation; d, deletion

leads to the overexpression of a novel tyrosine kinase termed anaplastic lymphoma kinase (ALK) located at 2p23[36–38] and is associated with good prognosis.

A wide variety of other numerical and structural abnormalities are observed in NHL whose exact biological significance remains to be determined. Nevertheless, it is clear that NHLs with markedly abnormal karyotypes are associated with inferior survival[39].

Cytogenetics and diagnosis: small round blue cell tumours

Small round blue cell tumours may present to almost any surgical specialty because primary sites include the orbit, facial sinuses, head and neck, chest, abdomen, pelvis, testis and limbs. This group of tumours includes the peripheral primitive neuroectodermal (pPNET) family, neuroblastoma, rhabdomyosarcoma and lymphoblastic lymphoma[40]. Although light microscopy combined with immunohistochemistry allows a specific diagnosis in the majority of cases, tumours with little evidence of differentiation continue to cause diagnostic dilemmas. Identification of tumour-specific chromosomal translocations may potentially help in differentiation of pPNET family and alveolar rhabdomyosarcomas.

The pPNET family of tumours includes tumours previously identified as Askin tumours and Ewing's sarcoma[41]. These tumours all express translocations involving the *EWS* gene located at chromosome 22q12 (*Table 2*). Three translocations known as EWS-FLI-1[42,43], EWS-ERG and EWS-ETV1[44–46] affect more than 95 per cent of all tumours classified as pPNET. If the presence of specific cytogenetic translocations is to be the *sine qua non* of this tumour group, effective diagnostic strategies must be available for their detection. This requires the availability of fresh tumour tissue for tumour cell karyotyping. Diagnostic procedures, such as FISH using fresh tumour imprints[47] and RT–PCR[44,48] using RNA extracted from fresh-frozen tumour material, may provide alternative methods of diagnosing these tumours. These techniques are currently restricted to specialist centres. However, availability of stored tumour samples frozen at −70°C may be particularly useful when diagnostic difficulties occur.

Like the pPNET family of tumours, desmoplastic small round cell tumours have a characteristic translocation. In these tumours the Wilms' tumour gene 1 at chromosome 11p13 is fused with the *EWS* gene at chromosome 22q12[49]. These tumours are classically diagnosed on the basis of microscopic appearance combined with immunohistochemical evidence of epithelial, neural and muscle differentiation[50]. Fresh tissue may be helpful in diagnosing this difficult tumour, either by classical cytogenetic or RT–PCR analysis. Availability of stored fresh-frozen tissue is essential for establishing the frequency of this translocation in desmoplastic round cell tumours. If such studies demonstrate a consistent abnormality involving the *EWS* gene, it may improve our understanding of the biology of this tumour and suggests that chemotherapy regimens similar to those used for the pPNET family of tumours could, perhaps, be more effective than other soft tissue sarcoma protocols.

Cytogenetics and prognosis: rhabdomyosarcoma and neuroblastoma

Rhabdomyosarcomas are soft tissue sarcomas which exhibit variable evidence of skeletal muscle differentiation. Although well differentiated tumours with obvious rhabdomyoblasts containing visible cross-striations like those of mature skeletal muscle are relatively easy to diagnose, undifferentiated tumours are difficult to classify using conventional histological techniques. Histologically, rhabdomyosarcomas may be broadly divided into two subtypes, alveolar and embryonal[51]. Tumours of alveolar subtype carry a worse prognosis than embryonal tumours[51,52]. However, differentiation of alveolar from embryonal tumours may be difficult because many tumours have only focal areas with classical alveolar cells. In addition, a solid alveolar variant which previously may have been diagnosed as embryonal has been identified recently[53].

Cytogenetic analysis of rhabdomyosarcomas has revealed several characteristic changes which may help the clinician make a diagnosis. This is particularly important because, in an attempt to improve long-term survival, patients with alveolar tumours receive more intensive chemotherapy than those with an equivalent stage embryonal tumour. Cytogenetic analysis of alveolar rhabdomyosarcomas has revealed that nearly all tumours have one of two characteristic translocations, t(2;13)(q35;q14) or t(1;13)(p36;q14), which produce transcriptionally active fusion proteins known respectively as PAX3-FKHR and PAX7-FKHR[54,55]. These translocations may also be detected using FISH[56] or RT–PCR[57] technology. Although a specific gene abnormality associated with embryonal rhabdomyosarcomas has not been identified, approximately 90 per cent of tumours have loss of heterozygosity of chromosome 11p15, identification of which would support the diagnosis of embryonal subtype[58].

Histological appearance and measurement of urinary catecholamines are usually diagnostic of neuroblastoma. However, the disease exhibits marked differences in aggressiveness, mirrored by heterogeneous biological characteristics[59]. Tumours which are hyperdiploid appear to carry a better overall prognosis[60], while deletion of chromosome 1p36·2–3 and amplification of the *MYCN* gene are associated with poor prognosis[61,62]. These abnormalities can be detected using cytogenetic, FISH and RT–PCR[63–65] methods. In future, it may be possible to use less toxic chemotherapeutic regimens than are currently employed for those with favourable biological characteristics.

Genetics and screening: pancreatic carcinoma

Pancreatic adenocarcinoma is the fifth most common cause of cancer death in the USA. Typically an aggressive carcinoma, it has an overall 5-year survival rate of less than 5 per cent. However, patients with small tumours (less than 2 cm) that are completely excised and have no evidence of disease dissemination or blood vessel invasion fare better, with 5-year survival rates of 20 per cent[66–68]. An improved understanding of the molecular changes responsible for the development of pancreatic cancer may lead to novel strategies allowing diagnosis and treatment at an earlier stage in the disease process.

Pancreatic carcinoma arises as part of defined genetic syndromes, namely hereditary pancreatitis[69], ataxia telangiectasia[70], hereditary non-polyposis colorectal cancer (HNPCC or Lynch syndrome II)[71,72] and familial atypical mole-malignant melanoma (FAMMM) syndrome[73] (*Table 1*). However, patients with apparently sporadic pancreatic carcinoma are significantly more likely to have a close relative with the disease (7·8 *versus* 0·6 per cent in controls)[69,71–73].

The mechanisms by which hereditary genetic syndromes predispose to pancreatic carcinoma are gradually being elucidated. Patients with ataxia telangiectasia are thought to have a mutation in the DNA repair pathway which predisposes to accumulation of mutated DNA sequences[74]. The genetic mutations in HNPCC appear to predispose to tumour development by mutations in the human mismatch repair system[75–78]. In FAMMM, mutations of *p16* may result in loss of normal control of cell division[73,79,80].

Oncogenes were the first gene family identified in tumorigenesis. These genes are mutated forms of normal cellular proto-oncogenes which result in the gene being permanently switched on. In pancreatic carcinoma, one member of the *ras* oncogene family, K-*ras*, is mutated in up to 85 per cent of tumours[81–83]. Papillary and atypical forms have the highest frequency of mutations, whereas flat mucinous lesions have the lowest rate. The near universal occurrence of a specific gene mutation in pancreatic cancer and the high frequency of mutation in lesions regarded as precursors of pancreatic malignancy are highly suggestive that changes in the K-*ras* gene are an early event in the neoplastic process. Development of diagnostic techniques to allow reliable non-invasive detection of asymptomatic tumours currently offers the best opportunity of reducing the mortality rate from this disease. Indeed K-*ras* mutations can be detected using PCR technology in pancreatic juice[84,85], peripheral blood[85] and stool samples[86]. Clearly, before the widespread introduction of screening for asymptomatic pancreatic carcinomas is undertaken, objective evidence that this improves outcome must be available. Any benefit in terms of reduced tumour mortality rate must be balanced against operative mortality rates which average 6·4 per cent and morbidity rates which vary between 25 and 40 per cent[66–68].

Cytogenetics and cancer prevention: medullary thyroid carcinoma

There is increasing interest in the influence of genetic factors in the development of malignancies in adult life. Some people carry germline gene mutations which predispose them to development of a specific cancer or group of cancers (*Table 1*). Although only a minority of people with cancer will have a well defined cancer syndrome, in 5–10 per cent of families with cancer genetic predisposition will contribute to tumour development[87]. Family studies can add a great deal to our understanding of genetic alterations in cancer as the same genes are often involved in sporadic neoplasms.

For families with multiple endocrine neoplasia (MEN) type 2, the potential to prevent death from medullary thyroid carcinoma (MTC) by detection of premalignant changes within the thyroid has been recognized for many years[88,89]. MTC may arise sporadically or as part of three well defined clinical syndromes: MEN types 2A, 2B and familial MTC (*Table 3*)[88]. MTC develops from thyroid C cells, with development of C-cell hyperplasia preceding the appearance of MTC. The established screening programme for MTC requires yearly analysis of baseline and

Table 3 Features of syndromes associated with development of medullary thyroid carcinoma

Clinical features	MEN2A	MEN2B	Familial MTC
MTC	All at risk	All at risk	All at risk
Age at onset	Typically 15–70 years	Typically < 15 years	Late onset
Disease pattern	Variable	Aggressive	Indolent
Phaeochromocytoma (%)	50	50	—
Parathyroid hyperplasia/ adenoma (%)	10–40	—	—
Inheritance	AD, high penetrance	AD, frequently new mutation	AD

MEN, multiple endocrine neoplasia; MTC, medullary thyroid carcinoma; AD, autosomal dominant pentagastrin-stimulated levels of calcitonin in those known to be at risk[89]. Although the majority of patients with MEN2A at risk of developing MTC do so between the second and fourth decades of life, recent reports from the USA highlight disease occurrence in the first decade of life[90]. More importantly, by the time raised calcitonin levels are detectable, 80 per cent have 'benign' C-cell hyperplasia and multiple foci of microscopic carcinoma. Following thyroidectomy patients with microscopic MTC remain at risk of developing clinically detectable metastatic disease if followed for long enough[90]. Clearly, the current standard management of families with MEN2A is unsatisfactory. In addition, it is wasteful of resources as on average 50 per cent of those screened are not at risk because MEN2A is inherited in an autosomal dominant fashion[88].

Recent advances in our understanding of the genetics of MEN2A may allow improved care for affected families as mutations of the *RET* gene located on chromosome 10q11 have been reported in this syndrome. These mutations can be identified in peripheral blood samples using currently available technology[88,90,91]. It is estimated that patients who have an abnormal *RET* gene have a greater than 70 per cent chance of developing MTC during the first four decades of life. Genetic analysis may be performed on cord blood, allowing early prophylactic thyroidectomy. However, genetic screening should only be carried out following appropriate family counselling because of the potential risks of increasing anxiety. In addition, families offered prophylactic thyroidectomy should be aware that it is far too early to be certain if early thyroidectomy will fulfil the role of screening in preventing development of incurable metastatic disease. The potential adverse affects of genetic screening will, however, be offset by reduced familial anxiety as 50 per cent of those currently being screened for development of MTC, hyperparathyroidism and phaeochromocytoma will be found not to be at risk.

Approximately 20 per cent of apparently isolated cases of MTC act as index cases for previously unrecognized MEN kindreds[92]. For patients presenting with thyroid nodules, where MTC remains part of the differential diagnosis, snap freezing fresh tumour at the time of excision may allow retrospective analysis of the *RET* gene if the diagnosis of MTC is confirmed. A simple algorithm for suggested management of patients who may have MTC is shown in *Fig. 1*.

The genetic abnormalities for MEN2B and familial MTC also reside within the *RET* gene although they involve different mutations[88]. For families with MEN2B, in which the clinical behaviour of MTC is more aggressive and known to occur as early as the first year of life[93], management should follow that for MEN2A, although prophylactic thyroidectomy may be considered at a younger age. For familial MTC, the late onset and indolent nature of the condition may mean that genetic screening is unjustified. However, if required, the algorithm for MEN2A can be easily applied to this group of tumours.

Cytogenetics and cancer prevention: breast and ovarian cancer

Increasing public awareness of the possibility that breast and ovarian cancer may be inherited has been highlighted by the news media; as a result, patients and relatives will undoubtedly approach surgeons to find out more about individual risks. Clinicians involved in the care of such patients should be aware of the advances in our

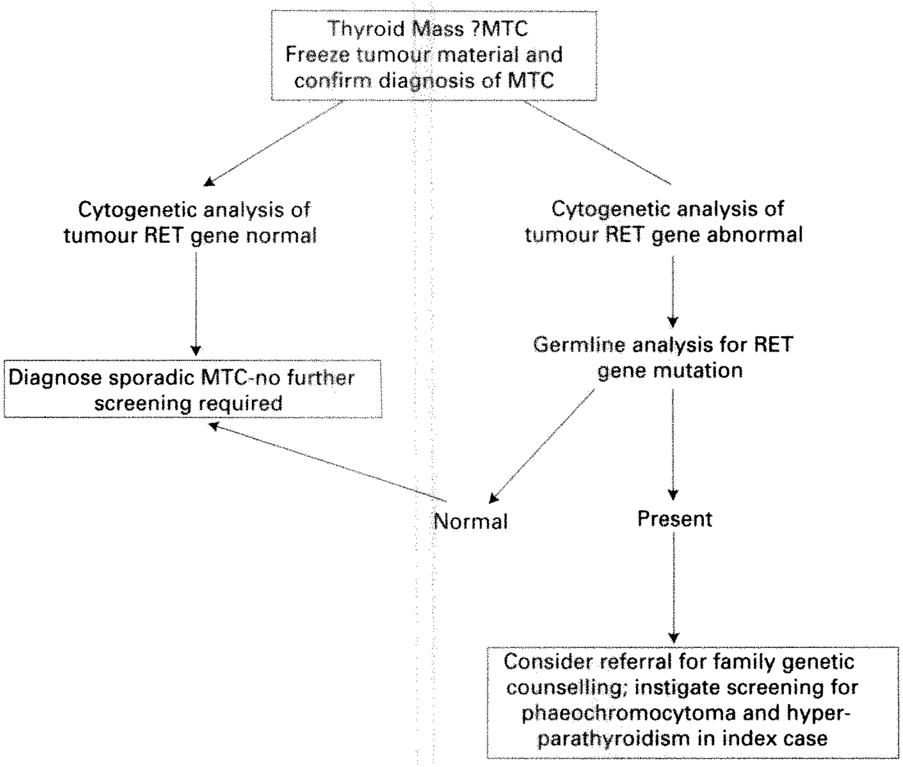
Thyroid Mass ?MTC
Freeze tumour material and confirm diagnosis of MTC
Cytogenetic analysis of tumour RET gene normal
Cytogenetic analysis of tumour RET gene abnormal
Diagnose sporadic MTC-no further screening required
Germline analysis for RET gene mutation
Normal
Present
Consider referral for family genetic counselling; instigate screening for phaeochromocytoma and hyperparathyroidism in index case

Fig. 1 Suggested algorithm for managing patients where medullary thyroid carcinoma (MTC) forms part of the differential diagnosis

understanding of tumour biology and risk of inheritance. While knowledge of the literature may provide the former, the latter requires the surgeon to have an active role in ensuring that relevant data for a given tumour are available for accurate genetic counselling. A careful clinical history, the age of onset and tumour type in first-, second- and third-degree relatives will help identify those who potentially have an inherited cancer risk.

Mutations of the *BRCA-1* gene located on chromosome 17q2 can be identified in around 60 per cent of ovarian and 40 per cent of familial breast cancers, although only 1–2 per cent of sporadic breast cancers and 3 per cent of patients with ovarian cancer have a germline mutation[16,94,95]. It has been estimated that between 1 in 300 and 1 in 800 are carriers of *BRCA-1* mutations, with heterozygotes having an 85 and 63 per cent lifetime risk of developing breast and ovarian cancer respectively[96]. In addition, the presence of *BRCA-1* gene anomalies carries a fourfold risk of developing colonic and a threefold risk of developing prostatic carcinoma. Mutation of a second breast cancer gene, *BRCA-2*, seems to carry a similar risk to *BRCA-1*[94,97] and appears to be involved in the development of male breast cancer[98].

Although it is possible to perform germline analysis *de novo* for all patients with breast or ovarian carcinoma, this would place a considerable workload on genetic testing departments for relatively little gain. Knowledge of tumour genetic abnormalities allows a significant reduction in the number of patients requiring germline analysis, although it undoubtedly still represents a significant workload and may have to be restricted to those who are identified as being at risk on the basis of family history. However, in the long term, availability of a large number of frozen tumour samples for retrospective genetic analysis may allow more specific assessment of risk for those who come forward for prophylactic mastectomy or oophorectomy where family members have died from these diseases.

Cytogenetics and cancer prevention: gastrointestinal malignancy

Tumours of the gastrointestinal system are among the most common tumours in man; although environmental influences have been clearly implicated, it has become increasingly apparent that there are also inherited risk factors. Familial adenomatous polyposis coli (FAPC)[99–101], ataxia telangiectasia[68,72] and HNPCC[73–76] predispose to development of adenocarcinoma of the stomach. In a small number of families an autosomal dominant pattern of inheritance has been reported. The majority of gastric tumours are apparently sporadic. However, there is an excess risk of first-degree relatives developing gastric carcinoma when the proband is less than 50 years old at the time of diagnosis, suggesting that an inherited risk factor may exist in these families[102]. Although structural and numerical abnormalities of a number of chromosomes have been identified in gastric tumours, a germline mutation which would allow development of screening tests has yet to be recognized[103].

Malignant tumours of the duodenum and small bowel are rare in comparison to malignancy of the colon. FAPC predisposes to the development of periampullary and small bowel carcinomas[99,100], Gorlin's basal cell nevus syndrome to carcinoid tumours[104] and neurofibromatosis[105] to neurofibromas and neurofibrosarcomas. Endoscopic surveillance of those known to carry the mutations characteristic of these conditions may be of value in detecting asymptomatic (early stage) disease.

The general population has a 6 per cent lifetime risk of developing colon cancer. The vast majority of these tumours are sporadic, with hereditary polyposis syndromes accounting for approximately 1 per cent and HNPCC for 5–10 per cent[99,100]. Currently all members of families known to have FAPC are screened for the appearance of polyps during the second to fifth decades of life, although the autosomal dominant pattern of inheritance means that only 50 per cent are at risk of developing the disease. FAPC is associated with abnormalities of the adenomatous polyposis coli gene (*APC*) located at chromosome 5q21[101], offering the possibility of germline screening for members of kindreds with familial polyposis coli. Gardner's syndrome and possibly Turcot's syndrome are other hereditary polyposis syndromes associated with abnormalities of the *APC* gene[99] for which genetic screening may also be possible.

HNPCC accounts for the majority of inherited colonic carcinomas. The genetics of this hereditary syndrome are gradually being elucidated, with four candidate genes identified[73–76] (*Table 1*). Those known to be at risk of developing colonic carcinoma require regular screening by endoscopy. Again, an autosomal dominant mode of transmission means that only 50 per cent of those screened are actually at risk of developing the disease. Identification of specific gene abnormalities may allow targeting of screening programmes to those known to carry the mutated gene, and may in the future allow prophylactic colectomy at an earlier stage in the disease process.

Conclusion

Over the past decade there have been considerable advances in tumour molecular and cytogenetic analysis which may help in the diagnosis, treatment and prevention of cancer. Cytogenetic analysis of tumour material has identified specific translocations in many rare sarcomas (*Table 2*). The identification of diagnostic chromosome translocations in histologically undifferentiated tumours may support a diagnosis which is doubtful on histological grounds alone, or may lead to a reconsideration of the histological diagnosis. In addition, cloning of the breakpoints involved in lymphoma- and sarcoma-associated translocations opens up new opportunities for molecular diagnosis and detection of minimal residual disease. Tumour cytogenetics is likely to play an increasingly important part in directing cancer therapy. However, most techniques currently available for cytogenetic analysis are only suitable for use on fresh tumour material. Surgeons should consider the implications of routinely placing tumour samples in formalin before sending them to the pathology department.

The United Kingdom Children's Cancer Study Group (UKCCSG) has recommended for many years that any tumour arising in childhood that is biopsied or excised should be submitted for cytogenetic analysis, cryopreservation and routine histological analysis. To ensure that UKCCSG recommendations are carried out, all surgeons operating on children with potential tumours should make appropriate arrangements with their pathology department before tumours are excised.

For adult patients the situation is much less clear. For families with a known cancer predisposing syndrome

(*Table 1*) tumour material should ideally be submitted for cytogenetic analysis and cryopreservation. When a tumour is likely to be a sarcoma, cytogenetic analysis may prove invaluable in making a diagnosis (*Table 2*) and submission of fresh tumour tissue should be considered.

Surgical specimens require to be divided so that portions can be submitted for cytogenetics and cryopreservation, as well as for routine histological analysis. As correct handling of tumour samples is essential for cryopreservation which will allow analysis by RT-PCR, and for cytogenetic analysis by karyotyping or FISH on tumour imprints, the pathologist requires advanced warning. In the operating theatre, tumour samples should not be placed in formalin. Instead they should be sent dry or wrapped in foil (not filter paper which induces dehydration artefacts) for the immediate attention of the pathologist. Undue delay in cryopreservation must be avoided at all costs, as RNA used for RT-PCR analysis is rapidly degraded in samples left at room temperature. Where facilities for handling specimens for long-term cryopreservation and cytogenetic analysis are not available, patients should be referred to a centre where such facilities exist. Routine submission of fresh tumour material from most patients with carcinoma at the present time would impose impossible pressures on pathology and genetic resources. The benefit would, in any event, be uncertain as at present most genetic events associated with tumour development appear not to be inherited.

As our knowledge of tumour biology increases, more sophisticated cytogenetic and molecular analysis of human tumours will be needed; provision of facilities outside specialist institutes will have to be considered.

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Review

Port-site metastases following laparoscopic surgery

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Background Application of laparoscopy to the resection of malignancy has been followed by a literature describing cases of metastatic involvement at laparoscopic port sites. These include patients who underwent surgery for early stage carcinoma and instances following laparoscopic procedures during which tumours were not dissected.

Methods Recently published clinical and experimental studies, and case reports related to this problem are reviewed; their relevance is discussed.

Results Experimental studies incorporating bench top and large animal models have confirmed that tumour cells may be redistributed to port sites during laparoscopic surgery either directly from contaminated instruments or indirectly via the insufflation gas. Small animal models suggest that the incidence of wound metastasis is increased following conventional laparoscopic surgery, and that it may be decreased by gasless laparoscopy or helium insufflation. This evidence suggests that the development of port-site metastases depends not only on the physical redistribution of tumour cells but also on the specific insufflation gas used, possibly because of influences on local metabolic or immune factors acting at the wound site.

Conclusion Further research in this area is urgent. Until the issue is better understood, patients undergoing laparoscopic surgery for malignancy should be entered into clinical trials.

Since the first report of metastasis to a laparoscopic port site by Döbrönte *et al.*[1] in 1978, it has become increasingly clear that the laparoscopic manipulation of both abdominal and thoracic malignancies may be followed by metastasis to surgical access wounds. Whether this is more likely following laparoscopic than open surgery is controversial[2–4]. However individual case reports, as well as the results of recent experimental studies[5–9], suggest that this problem is significant.

A critical review of the issue is warranted, as laparoscopic techniques, while attractive in terms of cosmesis, shorter hospital stay and reduced postoperative pain[10], cannot be justified if they result in an incidence of recurrent malignant disease in surgical access wounds which compromises long-term outcome. Wound seeding of a potentially curable malignancy is a disaster which may change a curable condition into an incurable one. Furthermore, recurrence after palliative laparoscopic resection may compromise quality of life. Consequently, many surgeons have expressed concern about the appropriateness of the application of laparoscopic techniques to the surgical treatment of malignancy[2,3,9,11].

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Evidence from clinical cases

Since 1978, in excess of 100 reports of metastasis to laparoscopy wounds have appeared in the surgical and gynaecological literature[12]. These include instances of metastasis following diagnostic laparoscopy or laparoscopic resection of carcinoma of the gallbladder[3,13,14], ovary[1,15,16], pancreas[4,17], colon[18–20], bladder[21,22], stomach[23] and liver[24]. Of concern are reported instances of metastasis following laparoscopy when it has been documented that the primary tumour was not manipulated during the procedure[17,25] as well as metastasis following laparoscopic colectomy for Dukes A colonic lesions[20,26], mucosal gallbladder cancer[6] and carcinoma *in situ*[3] (*Tables 1* and *2*). It is also important to realize that this problem is not exclusive to laparoscopy; it has also been associated with thoracoscopic cancer resection[29,31,32].

Following the early case reports, Nduka *et al.*[2] published the first review of the problem in this Journal in 1994, describing a collected series of 20 cases, all adenocarcinomas. Wibbenmeyer *et al.*[3] in 1995 reviewed a population undergoing laparoscopic cholecystectomy and reported a 1 per cent incidence of gallbladder cancer in the patient group studied. Laparoscopic cholecystectomy was associated with an increased risk of dissemination and

Table 1 Case reports of port-site metastases developing following laparoscopic surgery without tumour manipulation

Reference	Year	Procedure	Tumour type
Siriwardena and Samarji[4]	1993	Laparoscopic cholecystectomy	Pancreatic adenocarcinoma
Watson[17]	1995	Laparoscopic gastroenterostomy	Pancreatic adenocarcinoma
Nieveen *et al.*[27]	1996	Diagnostic laparoscopy	Pancreatic adenocarcinoma
Jorgensen *et al.*[25]	1995	Diagnostic laparoscopy	Pancreatic adenocarcinoma
Nieveen *et al.*[27]	1996	Diagnostic laparoscopy	Pancreatic adenocarcinoma
Nieveen *et al.*[27]	1996	Diagnostic laparoscopy	Stomach adenocarcinoma
Nieveen *et al.*[27]	1996	Diagnostic laparoscopy	Liver tumour

Table 2 Case reports of port-site metastases developing following laparoscopic excision of an early 'curable' tumour

Reference	Year	Tumour type	Stage
Prasad *et al.*[20]	1994	Colon adenocarcinoma	Dukes A
Lauroy *et al.*[11]	1994	Colon adenocarcinoma	Dukes A
Fingerhut[26]	1995	Colon adenocarcinoma	Dukes A
Shepherd *et al.*[28]	1994	Ovarian carcinoma	'Borderline'
Fry *et al.*[29]	1995	Adenocarcinoma of lung	$T_1 N_0 M_0$
Nduka *et al.*[2]	1994	Gallbladder carcinoma	'Non-invasive'
Perracchia *et al.*[30]	1993	Oesophageal carcinoma	$T_2 N_0 M_0$

diffuse peritoneal seeding of tumour, compared with historical experience with open cholecystectomy. A retrospective analysis of 219 patients with ovarian cancer was reported by Kruitwagen *et al.*[33] in 1996. Seven of 43 of these patients developed tumour secondaries at port sites following a preliminary diagnostic laparoscopy. Martinez *et al.*[12] also reviewed the clinical literature in 1995. Their series comprised 105 cases: diagnostic laparoscopy (five), laparoscopic cholecystectomy (42), gynaecological surgery (13), colorectal surgery (34), thoracoscopic surgery (seven) and urological surgery (four).

Implantation of tumour following open resection of thoracic tumour is rare[31,34] and usually involves surgery for mesothelioma. Wound metastases following oesophagectomy are similarly uncommon[35]. Following the advent of thoracoscopic lung resection for malignancy, however, an increasing number of implantation metastases have been reported[29,31]. In 1996 Downey *et al.*[31] described 21 cases of wound dissemination of malignant tumours following video-assisted thoracic surgery. These occurred as a result of operation for both primary and secondary lung tumours. The majority of the port-site metastases were adenocarcinomas, although squamous cell carcinoma, small cell carcinoma, medullary carcinoma of the thyroid and melanoma were also recorded. Port-site metastasis has also been reported following minimally invasive oesophagectomy[31,32].

The incidence of tumour involvement of the laparotomy wound in patients undergoing open colectomy for carcinoma is less than 1 per cent according to both Hewett and Baxter[36] and Hughes *et al.*[37]. Reilly *et al.*[38], in a prospective study of 1711 patients undergoing open colon cancer resection, found the incidence of this complication to be 1·5 per cent. By contrast, both Wexner *et al.*[39] and Prasad *et al.*[20] estimate that the incidence of wound metastasis following laparoscopic colectomy is approximately 4 per cent. However, all of these estimates are crude and, in the absence of better data to define both the actual number of port-site recurrences in the community (numerator) and the number of laparoscopic resections (denominator), the exact incidence remains unknown. Because of the limitations of data collection methodology (perhaps with the exception of that of Reilly *et al.*), it is possible that historical estimates of the incidence of wound metastasis following open surgery have been underestimated.

Clinical presentation of port-site metastases and prognostic significance

The period between laparoscopic surgery and the clinical finding of a wound metastasis varies. It may occur as early as 7 days after operation[23,40], but most lesions arise between 3 and 9 months later[2,12,33,41]. Metastases typically present as hard, painful nodules at the previous site of one or more of the laparoscopic cannulas[2,12]. Kruitwagen *et al.*[33] assessed the effect of port-site metastasis on patient survival and found that the presence of a metastasis at the site of a trocar or paracentesis access wound correlated adversely (although not statistically significantly) with survival. This analysis was performed following adjustment of data for factors such as age, tumour stage, pre-existing illness and tumour histology.

It has been proposed that the development of port-site metastases correlates with the aggressiveness of the primary tumour and/or its stage[17,33], i.e. it is a prognostic indicator which is independent of the surgical approach (*Table 3*). However, laparoscopic surgery for tumours with low metastatic potential, such as a borderline ovarian tumour[28] or Dukes A colon carcinoma[20,26], has resulted in this phenomenon, suggesting that outcome may be adversely affected (*Table 2*).

Table 3 Interpretations of port-site metastasis

The incidence of metastasis is similar to that associated with open surgery
Metastases are more common following laparoscopy, but reflect the preoperative prognosis of the tumour. They do not adversely affect outcome
Metastases occur in patients who might otherwise have expected to have been disease free following open surgery. Prognosis is adversely affected

Experimental models

A number of experimental studies which seek to improve understanding of port-site metastasis have been reported recently. The models are usually one of three types. *In vitro* studies may be used to evaluate cell movement during laparoscopy[42,43]. These models are somewhat artificial and it is difficult to extrapolate results obtained in a rigid plastic pseudoabdomen to the clinical setting. Animal models are more analogous to clinical situations. Large animals (usually pigs) have been used to test for cell movement during laparoscopy using either radiolabelling techniques or micropore filters combined with cytological examination[43–45]. While the volume of the pig abdomen closely resembles that of the human, the lack of native tumour lines precludes testing for the endpoint of tumour growth. Nevertheless, these models may be useful for studies which map the intraoperative movement of tumour cells during laparoscopy.

Small animals (mice, rats, hamsters) have also been used[46–48]. Inbred, immune competent strains with native tumour lines[9,47,49], or immune compromised strains with human cancer cells[7,45], allow the endpoint of tumour growth to be tested. While the peritoneal cavity is much smaller than that of the human, these models can be used to examine variations in the laparoscopic environment rather than the simple mechanical manipulations tested in larger animals.

Evidence from *in vitro* and large animal models confirms that tumour cells are delivered to port sites via the laparoscopic environment[42–44,49]. There is little doubt that direct spread by contaminated instruments can account for this[44,50,51]. The role of tumour cells in aerosols causing indirect transfer to port sites is more controversial. Such aerosols have been demonstrated in a pig model[52] but their occurrence alone is not adequate evidence that they are responsible for the development of tumour metastasis[53]. Studies in small animal models have demonstrated a threefold to fivefold increase in the incidence of wound metastasis following laparoscopy with carbon dioxide compared with laparotomy[9], and adverse patterns of tumour growth following carbon dioxide pneumoperitoneum[49].

Effect of laparoscopy on tumour growth

It is believed that primary tumour growth rates are influenced by the degree of operative trauma[54,55], largely through the depressant effect that the latter exerts on systemic immunity[56–61]. Laparoscopy, because it creates less access-related trauma, may cause less suppression of immune function and so be less likely to facilitate tumour growth[61,62]. Allendorf *et al.*[60,63,64] support this concept. They demonstrated in a mouse model that tumour cells inoculated into the dorsal skin grow more easily and aggressively after laparotomy than after laparoscopy with carbon dioxide insufflation. This suggests a benefit in favour of laparoscopy in the treatment of malignant conditions. However, it is important to note that this study examined only extraperitoneal tumour growth. Interestingly, when Griffith *et al.*[65] investigated the effect of surgery on immune function by examining the effect of open and laparoscopic operation on natural killer cell cytotoxicity, they found a similar degree of immune suppression in both groups.

Others have used a rat model with the introduction into the peritoneum of free cancer cells to show that, while the presence of a port may predispose to port-site metastases, the presence of a pneumoperitoneum does not in itself enhance the implantation of free cancer cells[47]. In this study, however, insufflation was for only 10 min, which limits the time that pneumoperitoneum had to exert any possible adverse effect. In contradistinction to this, Voltz *et al.*[56] have demonstrated that the induction of a carbon dioxide pneumoperitoneum results in an increased seeding rate of intraperitoneal tumour cells, and also increases both the number and size of intra-abdominal metastases. This suggests that laparoscopy might result in a worsening of prognosis compared with laparotomy. Mathew *et al.*[9] demonstrated increased growth of a lacerated 'primary' tumour following laparotomy compared with laparoscopy, but significantly fewer wound metastases. It remains to be proven that the systemic immunological benefit of the laparoscopic approach has clinical merit as it is possible that adverse local factors associated with laparoscopy lead to early tumour recurrence in wounds.

Mechanisms of metastasis

Several possible explanations for the occurrence of port-site metastases have been proposed; it is likely that the aetiology is multifactorial (*Table 4*). Most contributing factors seem specific to the laparoscopic environment, although evidence supporting current understanding of this problem has been derived exclusively from animal models (*Table 5*). Cells may implant in wounds because of direct contact with contaminated laparoscopic instruments[2,44,67]. Frequent changes of instruments may predispose to this[44,50], and extraction of the tumour through a port wound may lead to coating of the port site with viable tumour cells[2,44,50]. This may be particularly relevant when extracting a relatively large tumour through a small access wound, where traumatic manipulation of the tumour may predispose to a substantial release of cells. It has also been suggested that direct contact between the abdominal wall and tumour may occur during periods of temporary loss of pneumoperitoneum[44,45].

Table 4 Possible mechanisms which lead to port-site metastasis

Mechanical		
	Direct contamination	
		Seeding during extraction of tumour through a small wound
		Seeding by contact with instruments contaminated with tumour cells
	Indirect contamination	
		Seeding into the wound during episodes of desufflation of the pneumoperitoneum
		Cells exist in an aerosol and are transferred to wounds and ports without direct contamination (chimney effect)
Metabolic/immunological		
		Seeding occurs in both open and laparoscopic wounds, but metastases are more likely after laparoscopy because of locally acting immunological and/or metabolic factors
Haematogenous		
		Seeding by haematogenous spread during surgery

Table 5 Information obtained from experimental models

In vitro/ex vivo studies	
	Ports and instruments are easily contaminated with tumour cells during laparoscopic surgery by direct contact[43]
	Tumour cells existing in aerosols have not been demonstrated[53]
Large animal studies	
	Ports and instruments are easily contaminated with tumour cells by direct contact[44,45,50]
	Tumour cells in aerosols have been demonstrated in some studies[52]
Small animal studies	
	Laparoscopy is associated with less growth of 'primary' tumours, and less overall immune suppression[48,60]
	Carbon dioxide pneumoperitoneum results in adverse patterns of intraperitoneal tumour growth[46–49]
	The likelihood of wound metastasis is increased three to five times by carbon dioxide pneumoperitoneum[9]
	Wound metastasis is less likely following gasless laparoscopy[48,66]
	Helium laparoscopy may reduce the risk of wound metastasis[7,26]

The indirect spread of tumour cells to surgical access wounds has also been proposed as an explanation for the phenomenon. Viable tumour cells are liberated into the peritoneal cavity during the resection of malignancy by conventional techniques[67–70] and many believe that, in the presence of a pneumoperitoneum, these exfoliated cells can be carried in an aerosol to implant in the laparoscopy access wounds. Implantation of exfoliated cells has been demonstrated to occur during open surgery[37,67]. Laparoscopic techniques are inherently less dextrous than open surgery and this may predispose to an increased burden of exfoliated tumour cells.

Evidence from clinical case reports suggests that neither instrument contamination nor direct implantation of exfoliated tumour cells is likely to be the sole mechanism for this phenomenon. Port-site tumours have been reported at sites where direct contamination is improbable, and in cases in which the primary tumour was not manipulated. Watson[17] has described the development of multiple abdominal wall metastases from a pancreatic carcinoma after laparoscopic gastroenterostomy. In this instance the theory of direct implantation is not feasible as the lesser sac was not opened and the tumour was not manipulated. A similar case following laparoscopic cholecystectomy was reported by Jorgensen *et al.*[25].

Haematogenous spread of tumour from the primary lesion to the port site has also been proposed, but this is an unlikely mechanism. Murthy *et al.*[55] have demonstrated that, when tumour cells are injected intravenously, wound metastases are rare, although they do arise at sites of intra-abdominal surgical trauma. It is possible that the positive pressure environment in the peritoneal cavity during pneumoperitoneum, along with the spillage of cancer cells into the peritoneal cavity and on to raw surfaces, may lead to viable tumour emboli entering the circulation. However, if this were the case, one would expect an increased rate of tumour metastasis to the usual sites of secondary involvement as well as to access wounds.

Local factors at the sites of port placement may contribute to the localization of tumour metastases. It is known that tumour preferentially spreads to recently traumatized tissues and that malignant cells grow more easily in areas of high cellular proliferation[55]. While the intact peritoneum is resistant to tumour cell implantation[9,46], the port site provides a localized peritoneal breach and an area of high cellular proliferation associated with the healing wound. The associated local release of inflammatory regulators[54,58,71] may generate an environment which facilitates the subsequent development of tumour metastasis. This mechanism alone, however, does not provide a complete explanation for an increased incidence of port-site metastases associated with laparoscopic surgery. It is, however, possible that small wounds, such as those created by laparoscopic trocars, produce a different environment for healing than large laparotomy wounds. The immunological or inflammatory response in these two different types of wound may be dissimilar.

Pneumoperitoneum-specific factors

A major difference between an open laparotomy and a resection performed laparoscopically can be found in the provision of access space for both vision and operative manipulation. For laparoscopy this is generally achieved by the creation of a pneumoperitoneum, involving the introduction of gas under pressure into the peritoneal cavity. Factors specific to the pneumoperitoneum which may play a role in the development of port-site metastases include mechanical effects of gas under pressure, potential metabolic and immunological effects due to the insufflating gas, alterations in peritoneal humidity, stretching of the abdominal wall and peritoneal lining, possible electrostatic interactions with trocars and pressure–flow effects related to the use of insufflating gas.

Nduka *et al.*[2] have suggested that the pneumoperitoneum acts as a closed system through which airborne particulate matter must circulate, whereas during open surgery this particulate matter tends to be drawn away by the theatre ventilation system. This may result in 'trapping of viable tumour cells by moist peritoneal surfaces'[2]. A so-called 'chimney phenomenon' has also been proposed[45]. This invokes the development of a Venturi effect, whereby the insufflation of carbon dioxide causes turbulence which displaces tumour cells. These cells are concentrated from an aerosol as a result of the leakage of carbon dioxide alongside port sites. This results in tumour implantation[46,48,49,72]. Tumour cells from aerosols may adhere to ports via attractive forces (electrostatic or molecular) or be deposited on them from instruments. When a port is removed, these tumour cells may be wiped off and deposited within the port-site wound. It is also possible that carbon dioxide gas under pressure dissects between tissue layers at the port site, thereby causing additional trauma and allowing tumour cells to lodge between muscle, fascial and peritoneal surfaces.

The presence of a pneumoperitoneum also results in stretching of the abdominal wall. This may augment the release of inflammatory mediators, such as transforming growth factor alpha, which are involved in the healing of wounds and may also promote tumour proliferation[46,71,73,74]. It is possible that alterations to pressure and flow rates during laparoscopy could affect a series of complex local and systemic metabolic and immune responses which may in turn facilitate tumour survival and implantation.

Influence of specific insufflation gases

Experimental studies using small animal models have demonstrated that the incidence of wound metastasis is reduced by eliminating carbon dioxide insufflation by using gasless laparoscopy[48,66]. Watson *et al.*[66] suggest that the incidence following gasless laparoscopy is similar to that following laparotomy. These experiments imply that an effect specific to laparoscopic insufflation accounts for the increased incidence of wound metastases proposed from clinical reports. Most studies have utilized carbon dioxide as the insufflation gas with the assumption that the physical effects of carbon dioxide pneumoperitoneum account for wound metastasis. However, three recent experimental reports[7,75,76] detail the effect of different insufflation gases on tumour behaviour during laparoscopy; the data are somewhat conflicting. Jacobi *et al.*[7] report a series of *in vitro*, *in vivo* and *ex vivo* experiments using a rat model and colonic tumour line. While the insufflation of carbon dioxide resulted in greater tumour growth than that of a control group, helium had no tumour enhancing effect. Dorrance *et al.*[75], however, using a rat tumour cell line, report that the promotion of tumour growth by laparoscopy is independent of the insufflating gas; this study used an aggressive breast cell cancer line which may have minimized differences between the treatment groups. Neuhaus *et al.*[76] compared carbon dioxide, helium, nitrous oxide and compressed air as insufflation gases to facilitate the laparoscopic laceration of an implanted solid tumour in a rat model. The incidence of port-site metastases was significantly reduced in rats undergoing helium insufflation, compared with the other groups. Because helium is an inert gas which generates no adverse metabolic effects[77,78], this study suggests that the development of port-site metastases may be influenced by metabolic determinants as well as the physical redistribution of tumour cells by the laparoscopic environment.

Voltz *et al.*[56,71] have demonstrated that the pneumoperitoneum results in significant mechanical, ventilatory, cellular, hormonal and immunological changes, and that these are influenced by intra-abdominal pressure, the insufflation gas used and the duration of insufflation. The specific adverse effects identified include severe acidosis involving the peritoneal surface and the underlying connective tissue, disturbances in electrical surface charges, and the release of various mediators such as endotoxin. The severe acidosis generated by carbon dioxide pneumoperitoneum, combined with raised intra-abdominal pressure, may impair macrophage function[56,71]. The insufflation of carbon dioxide has also been shown to compromise intraperitoneal macrophage activity and depress immunological responses in CD-1 mice, compared with laparoscopy with air insufflation[73]. Supporting this, West *et al.*[79] recently noted that carbon dioxide can transiently inhibit the ability of peritoneal macrophages to secrete inflammatory cytokines, particularly lipopolysaccharide-stimulated tumour necrosis factor and interleukin 1. This effect was not noted with air or helium. Carbon dioxide is also irritant to the peritoneum and this, via the release of inflammatory mediators such as transforming growth factor alpha, may favour tumour implantation at the raw peritoneal surfaces created by laparoscopy access ports[71].

Prevention of cutaneous metastases

Although the causes of port-site metastases remain uncertain, many investigators have suggested preventive strategies. These include port-site protection[80,81], the use of prophylactic tumoricidal agents[2,12,82–84], wound 'sterilization'[85] and gasless laparoscopy[66].

Port-site protection involves the use of plastic bags or wound protectors to prevent direct contact between a resected specimen and the port site[2,80,81]. It is also sensible to avoid traumatic manipulation of tumours which may shed tumour cells into the peritoneal cavity, and to ensure that the incision through which the specimen is retrieved is wide enough to avoid further inadvertent shedding of tumour cells[12,86]. As clinical cases have been reported in which tumour recurrence has occurred at port sites other than those used to deliver the tumour, this strategy alone is unlikely to prevent all port-site tumours.

The use of tumoricidal agents to destroy viable intraperitoneal cells and so prevent their implantation was originally proposed for open surgery more than 30 years ago[87]. It has more recently been suggested as a strategy to prevent port-site metastases[2,12,82]. Tumoricidal agents may be delivered by parenteral or intraperitoneal routes[67,87–89]. The efficacy of intraperitoneal chemotherapy at the time of surgery for gastric and ovarian cancers has been demonstrated for conventional surgery[88–90]. Lavage of the peritoneal cavity with large volumes of 0·9 per cent saline has also been proposed[91] as a preventive strategy. At present no experimental or clinical evidence has been published to support the routine use of tumoricidal agents during laparoscopic surgery.

The excision of laparoscopic port sites following procedures which involve malignancy has been advocated[3,8]. The disadvantage is that it may negate a principal benefit of minimal access surgery, namely small wounds. It is also not certain that the resultant wounds would be any less likely to become involved with metastatic tumour than the original ones. The use of low-energy carbon dioxide laser light[85] has been described for the 'sterilization' of mastectomy fields to prevent wound recurrence. This has also been proposed for use in laparoscopic surgery, although supporting data are yet to be published[2].

Gasless laparoscopy, which provides laparoscopic access without positive pressure pneumoperitoneum, is feasible[66,92]. However, existing devices used to maintain a working space give rather poor access in the flanks, making colonic mobilization awkward during laparoscopic colectomy. Nevertheless, because experimental evidence suggests that avoiding pneumoperitoneum may significantly reduce port-site tumours[48,66], this strategy (along with helium insufflation) warrants further investigation.

Conclusion

Recent evidence from clinical cases and experimental studies confirms that the incidence of wound metastasis following cancer surgery is increased with the laparoscopic approach; its occurrence following treatment for early stage cancers suggests that prognosis may be adversely influenced. The problem occurs despite the apparent reduction in systemic immune suppression and primary tumour growth following laparoscopic treatment of cancer in experimental models. It is likely that the mechanism of wound metastasis is multifactorial. Laparoscopy can result in the mechanical redistribution of tumour cells directly by spread from contaminated instruments and indirectly due to the mechanical effect of the insufflation gas. Metabolic and immunological factors specific to carbon dioxide insufflation, acting locally at the port site, may also be important. While experimental studies support further clinical investigation of the roles of gasless laparoscopy and helium insufflation in laparoscopic cancer surgery, a role for tumoricidal agents remains speculative. Until the issue of laparoscopy-associated wound metastasis is fully understood, laparoscopic cancer surgery should take place only within the context of clinical trials.

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Review

Upper gastrointestinal disease in patients with familial adenomatous polyposis

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Background Upper gastrointestinal disease has become an important aspect in the management of patients with familial adenomatous polyposis (FAP).
Methods A review of the literature was carried out using Medline. Epidemiology, pathology and treatment options are considered.
Results and conclusion Despite the fact that over 90 per cent of patients with FAP develop duodenal adenomas, only 5 per cent go on to develop cancer. In the absence of methods to detect who is at risk of cancer, all patients undergo regular endoscopic surveillance at present. Chemoprevention in the form of drug therapy may be the answer to controlling the disease.

Despite screening and prophylactic surgery significantly improving the survival of patients with familial adenomatous polyposis (FAP)[1–3] their life expectancy remains lower than that of the general population[4]; cancer, desmoid disease and the long-term consequences of surgery are the three main reasons[1,3,5]. The upper gastrointestinal tract is the commonest site of cancer after prophylactic colectomy, probably because the duodenum is the second commonest site of polyp development after the colon[6].

Historical aspects

Gastric polyps in FAP were first described in 1895[7] and duodenal polyps in 1904[8]. The first description of a duodenal cancer was in 1935[9], gastric cancer not being reported until 1962[10]. In the 1960s interest in upper gastrointestinal polyposis grew[11], with Duncan *et al.*[12] suggesting as early as 1968 that all patients with FAP should undergo regular upper gastrointestinal surveillance to detect polyps, at that time by barium radiology[13]. This view did not catch on, even when endoscopy was introduced in the 1970s. Indeed patients were only investigated if they had symptoms, such as abdominal pain or unexplained anaemia, or if they had presumed family preponderance for upper gastrointestinal polyps. When reporting retrospectively, various centres reported that approximately 50 per cent of their patients had duodenal adenomas (*Table 1*). In 1989 two groups[23,24] reported prospective studies showing a much higher incidence, with 90 per cent or more patients with FAP having duodenal adenomas. Later studies have found somewhat less than this, but these studies have contained small numbers, or

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Table 1 Endoscopic surveillance of the upper stomach and duodenum

Reference	Year	No. of patients screened	Duodenal adenomas (%)	Gastric adenomas (%)	No. with upper gastrointestinal cancer	Type of endoscope used	Biopsies
Yao *et al.*[14]	1977	14	100	—	0	Forward viewing	Lesions only
Ranzi *et al.*[15]	1981	9	66	44	0	Forward viewing	Random biopsies
Jarvinen *et al.*[6]	1983	34	48	12	2	Forward viewing	Lesions only
Burt *et al.*[16]	1984	11	63	9	0	Forward viewing	Lesions only
Bulow *et al.*[17]	1985	26	46	3	0	Forward viewing	Lesions only
Shemesh *et al.*[18]	1985	17	47	29	0	—	Random biopsies
Tonelli *et al.*[19]	1985	24	58	12	0	Forward viewing	Lesions only
Kurtz *et al.*[20]	1987	41	20	0	0	Forward viewing	Lesions only
Sarre *et al.*[21]	1987	100	33	2	0	Side viewing	Lesions only
Alexander *et al.*[22]	1989	18	50	—	0	Side viewing	Lesions only
Spigelman *et al.*[23]	1989	102	92	5	0	Side viewing	Random biopsies
Iida *et al.*[24]	1989	20	90	—	1	Side viewing	Lesions only
Seow-Choen *et al.*[25]	1992	25	20	4	0	Forward viewing	Random biopsies
Church *et al.*[26]	1992	240	66	7	0	Side viewing	Lesions only
Goedde *et al.*[27]	1992	30	67	17	3	Forward viewing	Lesions only
Bulow *et al.*[28]	1995	310	64	—	1	Side viewing	Random biopsies
Sawada and Muto[29]	1995	35	40	26	1	Side viewing	Lesions only
Iida *et al.*[30]	1996	23	91	—	0	Side viewing	Lesions only
Bertoni *et al.*[31]	1996	25	72	—	0	Side viewing	Random biopsies
Marcello *et al.*[32]	1996	42	73	14	4	Forward viewing	Lesions only

were not prospective, or did not use side-viewing endoscopes with random biopsy.

Epidemiology

Adenomas tend to be noted in the duodenum approximately 15 years after colonic polyps occur[21,33,34], but this may simply reflect the time when they are sought. At presentation, clinicians tend (reasonably) to concentrate on the large bowel manifestations, turning only to duodenal surveillance as patient's age.

Outside FAP, duodenal cancer is rare, with an incidence of 0·01–0·04 per cent in the general population[35]. Men are more often affected, usually in the sixth decade. Polyposis is associated with a high frequency of duodenal or periampullary cancer with estimates of between 1 and 12 per cent[33,36], and men and women are equally affected. The average age at which the diagnosis of duodenal cancer is made is 50 (range 18–78) years[13,32,33,37–40], approximately 10 years after the expected development of colonic cancer in untreated FAP[41]. Life-table analysis of 222 patients who had undergone colectomy and ileorectal anastomosis showed a 3·35 relative risk of dying compared with the general population, upper gastrointestinal malignancy being the commonest cause[4]. Pauli *et al.*[42] estimated the periampullary cancer risk to be 100–200-fold greater than that of the general population, and Offerhaus and colleagues[38] put the relative risk of duodenal adenocarcinoma at 331 and ampullary carcinoma at 124.

Gastric cancer risk is not increased in Western families, but is reported to be high in Japanese and Korean families with FAP. The increase in these countries is not simply related to the high background cancer rate, as patients with FAP have an observed:expected mortality ratio for gastric adenocarcinoma of 3·43 compared with the general Japanese population[43,44].

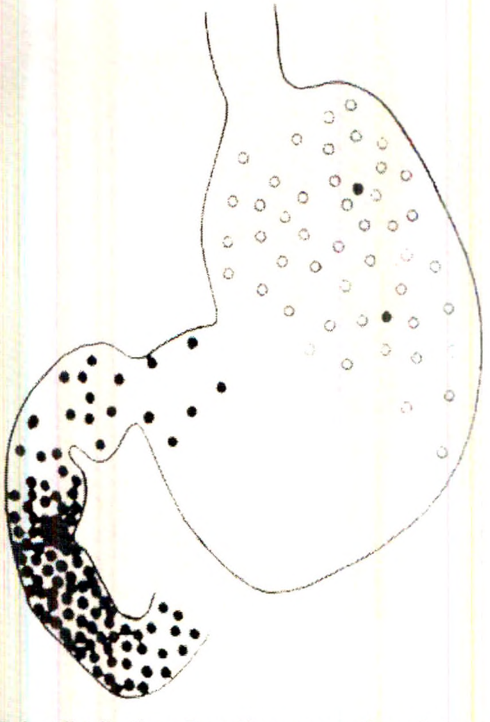

Fig. 1 Polyp distribution. Overall representation of sites affected by upper gastrointestinal polyposis. ○, Patient with fundic gland polyp(s); ●, patient with adenomas. (From Spigelman *et al.*[23]; reproduced with permission of The Lancet Ltd.)

Polyp distribution and type

Adenomas are distributed throughout the duodenum and small bowel, the majority being found in clusters around and distal to the ampulla of Vater[24,45]. Very few are found proximal to the ampulla compared with the number found in the second part of the duodenum. This distribution of polyps closely mirrors the pattern of mucosal exposure to bile (*Fig. 1*), an observation that has lead to studies relating bile metabolism to the pathogenesis of upper gastrointestinal polyps in these patients[23] (see below).

The macroscopic appearance of duodenal polyps is very different to that of colonic polyps. The number of the former varies from none visible to over 100. They may present as multiple discrete adenomas (1–10 mm in

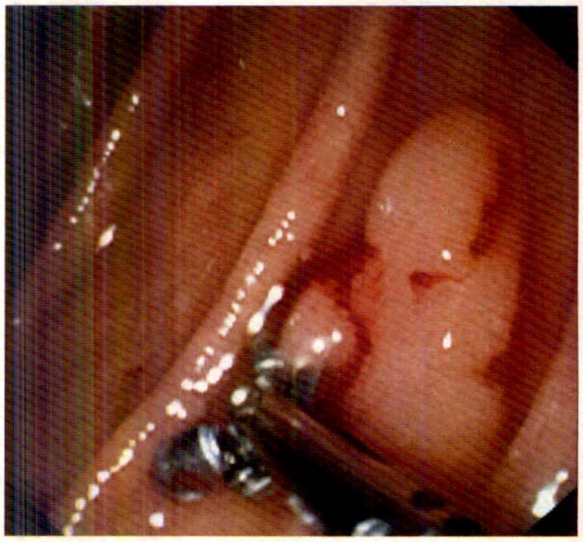

Fig. 2 Endoscopic view of the duodenum in familial adenomatous polyposis: discrete adenomas

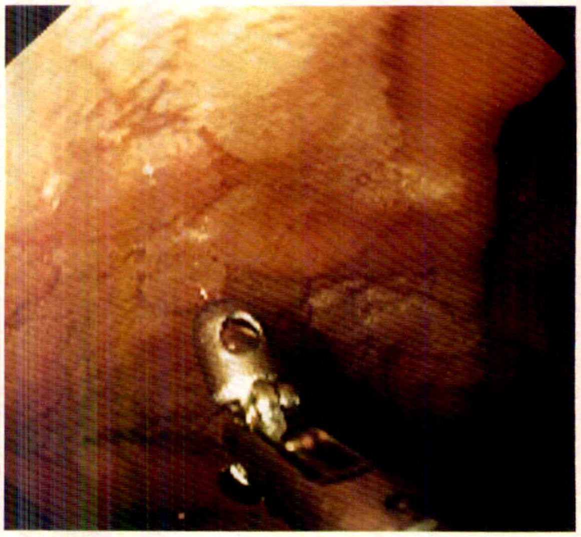

Fig. 3 Endoscopic view of the duodenum in familial adenomatous polyposis showing confluent adenomatous plaques

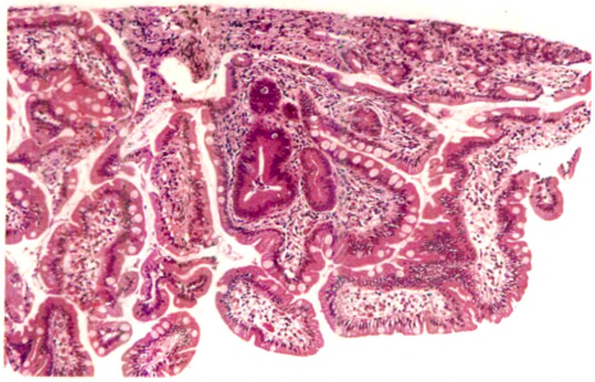

Fig. 4 Section from a biopsy of clinically normal mucosa showing a microadenoma in the centre of the photograph. (Haematoxylin and eosin stain, original magnification ×30)

Table 2 Staging system for severity of duodenal polyposis

	Duodenal disease grading (points)		
	1	2	3
No. of polyps	1–4	5–20	>20
Size of polyps (mm)	1–4	5–10	>10
Histology	Tubular*	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

*Or hyperplasia, inflammation. Stage 0, 0 points; stage I, 1–4 points; stage II, 5–6 points; stage III, 7–8 points; stage IV, 9–12 points

diameter) or as flat confluent plaques[30] (*Figs 2* and *3*). Sometimes no lesion can be seen and the only clinical abnormality is a prominent ampulla, or the mucosa may appear pale and seem to have a white covering which cannot be removed by rubbing[22]. Biopsies of apparently normal mucosa frequently show microadenomas (*Fig. 4*).

Duodenal polyps are microscopically adenomas, whereas most gastric polyps are histologically termed fundic gland. Duodenal adenomas that are small and tubular with minimal dysplastic features are at least risk of undergoing malignant change. The severity of duodenal polyposis can be quantified using a staging system developed by Spigelman and colleagues[23] which relies on clinical and histological assessment of the duodenum to provide a four-stage scoring system. Stages I and II signify mild duodenal polyposis whereas stages III and IV signify severe disease (*Table 2*).

Less than 10 per cent of patients have gastric adenomas. Although lesions which appear clinically to be polyps are found in the stomach of about 50 per cent of patients with FAP, these are mostly areas of cystic hyperplasia[16] on histological examination which, until recently, were thought to have no malignant potential[15,21]. There has, however, been a single case report describing the development of a gastric carcinoma from an area of fundic gland polyposis[46]. When gastric adenomas are present there seems to be a greater amount of bile reflux on scintigraphic duodenogastric reflux scanning[47]. Adenomatous polyps and malignancy have developed in all parts of the upper gastrointestinal tract, including the gallbladder[48] and biliary tree[49], suggesting that the entire intestinal epithelium is at risk in patients with FAP, especially areas exposed to bile[40].

Natural history

At St Mark's Hospital only 10 per cent of 102 patients with FAP undergoing endoscopic surveillance have been shown to develop advanced (stage IV) duodenal polyposis, while less than 20 per cent have very mild (stage I) disease. The remainder are divided equally between stages II and III. Of those patients who had repeat endoscopies (70 patients) over a mean of 40 (range 26–57) months, three developed duodenal cancer, having previously had advanced, but benign, disease. In seven patients the stage of duodenal polyposis also worsened (stage 0 to I in two patients, I to II in two patients, II to III in one patient, and III to IV in two patients). Patients with stage IV disease tend to be older, suggesting that duodenal polyposis is progressive. This is supported by prospective studies which have shown that the degree of polyposis worsens in 16–40 per cent of patients[22,24,50,51]. The changes are more apparent clinically than when histological assessment is taken into account[52].

Histologically confirmed upper gastrointestinal malignancy has developed in 25 patients from 20 families with FAP seen at St Mark's Hospital since 1925. Of these families, three had more than one member and one family had four members affected. The median age at which these cancers were diagnosed was 57 years and age at death was 58 years; these results are similar to those from the Mayo clinic[39]. Patients present with unexplained symptoms of weight loss, anaemia, jaundice or abdominal pain. When symptoms are present the median survival time is shorter, 5·2 months in the authors' series.

The adenoma–carcinoma sequence

Sellner[53] postulated from epidemiological results (differences in age between presentation with benign and malignant neoplasms, the similar ratios by sex and similar relative distributions within the small bowel) that the adenoma–carcinoma sequence was equally valid in the small bowel and duodenum. Case reports of patients with FAP who had been noted to have adenomatous polyps in association with duodenal malignancies also exist[37]. Spigelman *et al.*[54] examined a series of duodenal cancers in 47 patients with FAP and found remnants of adenoma as a component of, or adjacent to, the cancer in 45 of them. Villous adenomas were not surprisingly most commonly found in association with the cancers, highlighting their associated increased cancer risk.

Genetics

APC *mutations*

FAP is caused by germline mutations in one copy of the tumour suppressor gene, *APC*, localized to chromosome 5q22[55,56]. The gene contains 8538 base pairs and codes for a 300-kDa protein. There are 15 exons, 1–14 being small and exon 15 being much larger (6571 base pairs)[57]. The APC protein appears to affect cell adhesion through its association with the cadherin-binding protein, β catenin[58,59]. It is also thought to have a role in the cytoskeleton and thereby in cell division.

Many argue that there is genotype–phenotype correlation in FAP[60–63]. Different mutations result in different lengths of the final protein product which are more likely to have a differential effect on the protein's normal function. There are innumerable problems with demonstrating a sure effect, not least because of difficulties in accurately ascertaining the phenotype and in dealing with selection bias. For example, when counting polyps which should be counted and which ignored: macroscopic and easily visible polyps, those seen with the assistance of dye spray, or those seen at magnifying endoscopy or on histological examination? Does the resultant polyp count reflect the background absolute number or simply the visible growth fraction (the latter perhaps strongly influenced by environmental factors)? These difficulties also apply to ascertaining the true magnitude of duodenal polyposis. Other problems must also be considered. Was the study prospective? Was a side-viewing endoscope used (the equipment makes a difference)? Were random biopsies taken?

Given these caveats, it is thought that colonic polyps are more prevalent when mutations occur between codons 1250 and 1464, and death from colorectal cancer occurs earlier. Mutations at the extremes of the 3′ and 5′ part of the *APC* gene are probably associated with fewer visible polyps and delayed apparent onset of disease[64,65]. Upper gastrointestinal polyps do not appear to be more commonly associated with mutations between codons 1250 and 1464, but there may be family segregation in the occurrence of periampullary malignancy[34]. Preservation of duodenal disease in the absence of severe colonic disease or congenital hypertrophy of retinal pigment epithelium suggests that patients with mutations at any region of the gene are at risk of upper gastrointestinal disease[66]. This implies that in upper gastrointestinal disease there may be additional factors involved, such as other modifying genes or diet, so that gene analysis may not predict those at greatest risk of upper gastrointestinal cancer.

TP53 *mutations*

Mutations of the tumour suppressor gene *TP53* may help transform precancerous lesions to cancer. Overexpression of p53 has been correlated with increasing severity of dysplasia in colonic lesions[67]. The p53 protein can also be measured immunohistochemically, reflecting an increase in expression of *TP53* gene.

Endoscopic biopsies of duodenal polyps from patients with FAP and surgical specimens from upper gastrointestinal tract cancers have been examined for expression of p53[68], and *TP53* and K-*ras* status[69]. All cancers and 32 per cent of adenomas expressed p53, the intensity of staining increasing with dysplasia. The rates of mutation in *TP53* and K-*ras* are similar to those found in the colon, although the actual site of the *TP53* mutation is different, which suggests a different mutating agent, perhaps environmental or dietary. There is marked overexpression of p53 protein compared with the frequency of mutation suggesting functional inactivation of the gene maybe, once again, due to an abnormal cellular environment. It is possible that detecting overexpression of p53 protein will alert doctors to the need for more frequent surveillance.

Possible role of bile

Polyp distribution mirrors mucosal exposure to bile, suggesting a role for bile in duodenal adenoma development[23]. Several mechanisms are possible: increased mucosal absorption of carcinogens, mucosal damage leading to reactive hyperplasia with cell proliferation and an increased risk of a mutation[70], and supply of genotoxic compounds leading to second hit mutations of the *APC* gene (*Fig.* 5).

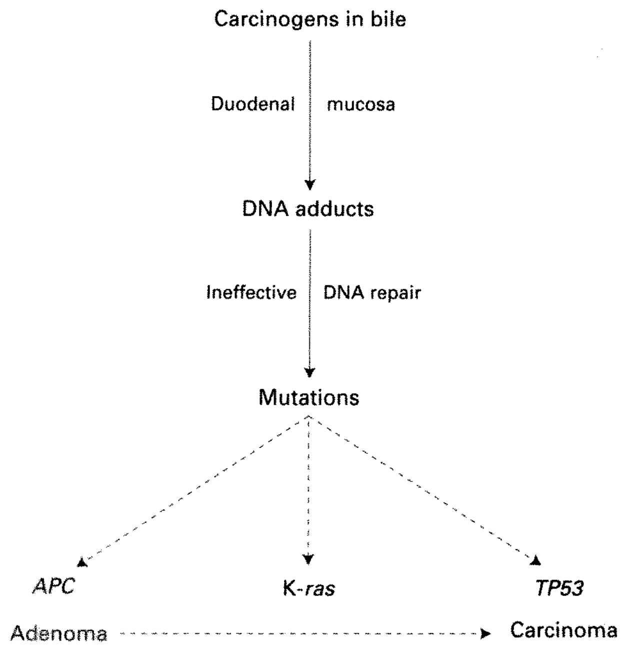

Fig. 5 Schematic representation of the role of DNA adducts in adenoma formation

DNA adducts are electrophilic molecules which bind covalently to DNA and, when not repaired, may lead to mutation and cancer. ^{32}P postlabelling detects DNA adducts and so acts as a fingerprint for the presence of mutating compounds, which may be of unknown composition and be present in very small quantities[71]. Human bile forms four major and characteristic adduct spots when it interacts with DNA. Duodenal mucosal biopsies from patients with FAP show these characteristic spots in much greater quantities[70]. These adduct spots are not simply the result of poor DNA repair in patients with FAP because they are seen when animal small intestine is challenged with FAP bile[72] and when DNA is mixed with FAP bile in a test tube[73]. Control bile from patients without FAP produces fewer adduct spots under these conditions. Furthermore, transgenic mice containing a mutation in the *Apc* gene also have bile which produces the same adduct pattern when incubated with DNA *in vitro*[74]. When FAP bile is incubated with human cell lines *in vitro* some mutagens require metabolic activation and some act directly. Adduct labelling also appears to be pH sensitive between a narrow band at pH 4–5, leading to therapeutic possibilities for upper gastrointestinal polyp prevention or treatment of FAP using antacids (see below)[75].

Pure biliary acids do not produce DNA adducts[76]. Bile *in vivo* is a complex mix of many substances other than bile acids and the finding of characteristic adduct spots and excess amounts of DNA adducts in FAP lends strong support to the presence of a biliary mutagen activated at a low pH. Perhaps the finding of abnormal liver metabolism of some carcinogens in FAP by glutathione S transferase mu[77], *N*-acetyltransferase and CYP 1A2[78] may go some way to explaining why polyposis bile is different.

Bile acids themselves also interact with second messenger signalling systems which are activated in colorectal cancer and, perhaps, in upper gastrointestinal cancer. One method is through the release of arachidonic acid and the production of prostaglandin E_2[79]; a second is through the protein kinase system, known to be activated in colonic adenomas and carcinomas[80]. These signalling systems are closely involved in controlling cellular proliferation and so in tumour development. Studies in patients with FAP that have shown different concentrations of individual bile acids, perhaps as a result of total colectomy and altered secondary bile acid metabolism, may mean that the above mechanisms might be important in upper gastrointestinal polyposis in FAP[81–84].

Treatment

Endoscopic surveillance

Regular endoscopic surveillance at intervals of 6 months of the retained rectal stump after ileorectal anastomosis is routine to detect cancer and permit prompt treatment. As more about upper gastrointestinal disease in FAP is learned, the question of surveillance of the upper gastrointestinal tract must be readdressed with respect to: patient comfort and through this acceptance of repeated examination, maximization of information through videotaped side-viewing endoscopy (which permits proper evaluation and recording of the ampulla, the most commonly affected site[22,23]) with the generous use of biopsy, and the frequency of re-examination (which can only be considered in the light of therapeutic options).

Duodenoscopy with a side-viewing instrument is often unpleasant for the patient. Given the need for repeated re-examination, these patients are not suitable for training of the inexperienced clinician as they may default from further follow-up (and may even refuse rectal surveillance in the future as well). Patients should be well sedated and examination should follow a routine (*Fig. 6*). Endoscopy is relatively safe, although complications such as pancreatitis have been reported when multiple biopsies of the periampullary area are taken[85].

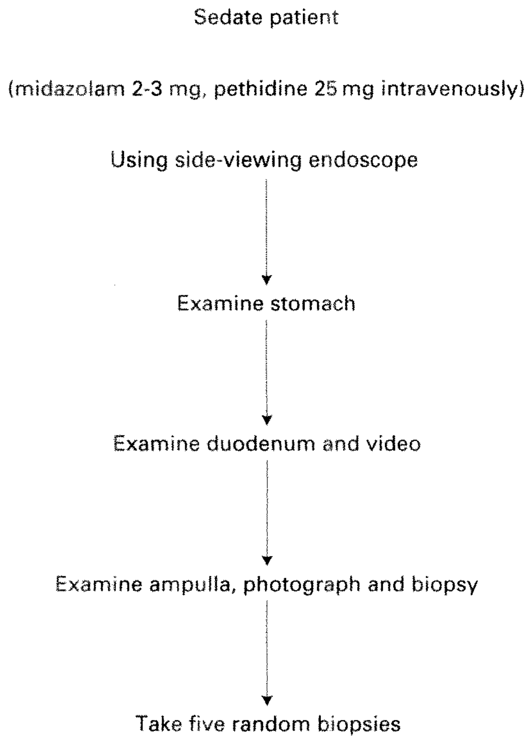
Sedate patient
(midazolam 2-3 mg, pethidine 25 mg intravenously)
Using side-viewing endoscope
Examine stomach
Examine duodenum and video
Examine ampulla, photograph and biopsy
Take five random biopsies

Fig. 6 Suggested protocol for upper gastrointestinal endoscopy in patients with familial adenomatous polyposis

Endoscopic ultrasonography may help when confronted by a huge or plaque-like polyp. Not only may it allow better selection of patients with invasive but operable lesions[86], it may also show lack of invasion in some cases, permitting further follow-up examination in 6 months rather than open surgery[87].

Treatment options

The aim is to control duodenal polyposis and thereby prevent the development of malignancy. The outcome after surgery for already established duodenal, periampullary or pancreatic malignancy is relatively poor. For example, the mean postoperative survival of patients with periampullary or duodenal cancer is 2 years for all stages of the disease[88]. The best results of 85 per cent 5-year survival occur only if the lesion is confined to the sphincter of Oddi[89].

Surgery. Surgical control by duodenotomy and mucosal excision of lesions seems at first sight a sensible preventative precaution when confronted by advanced but not invasive duodenal polyposis[90]. Review of 12 patients at St Mark's Hospital and the Hôpital St Antoine in Paris with stage IV polyposis, treated by duodenotomy and clearance, showed 100 per cent recurrence within 13 months of surgery[91]. Although this is not surprising in view of the presence of microadenomas, it makes management of advanced but non-invasive duodenal polyposis uncertain. This is why a case can be made for endoscopic ultrasonography and, in the absence of evidence of invasion, further surveillance in 6 months. Alternatively, duodenal excision by pancreas-sparing duodenectomy[92] may be suggested but this, and the even more aggressive Whipple's procedure, have such high associated morbidity and mortality rates that their application for benign disease may be questioned[93,94].

Endoscopy. Endoscopic control of duodenal polyps by snare excision or diathermy might seem obvious and easy[95]. However, duodenal polyps are often confluent, flat, plaque-like lesions, rather than discrete raised polyps, making snaring almost impossible (*Fig. 3*). Repeated periampullary diathermy may scar and narrow the ampulla, potentially leading to pancreatitis, haemorrhage, and future difficulties with clinical and histological assessment.

Photodynamic therapy. Photodynamic therapy (PDT) is a non-thermal means of inducing localized necrosis with light after administration of a photosensitizing drug. To treat gastrointestinal tract lesions, the photosensitizer must be given systemically, with the light delivered to the target area endoscopically. Good healing of PDT-treated lesions makes this approach at first glance attractive. However, although a range of photosensitizing drugs has been assessed by many groups, all have the drawback that patients may be left sensitive to bright light for several weeks after treatment[96,97]. Furthermore, treatment with PDT requires repeated application to remove all initial polyps followed by maintenance therapy. Photosensitivity and need for repeated treatment lessens the suitability of PDT. Even greater drawbacks, however, are the very superficial depth of necrosis achieved, the long illumination time required to treat each lesion, and the large numbers of lesions that need treatment in patients with clinically important upper gastrointestinal disease[98].

Argon plasma coagulation. Argon plasma coagulation is a method of non-contact electrocoagulation in which current is applied to tissue by means of ionized argon gas (argon plasma) that can be delivered endoscopically[99]. Coagulation depth is limited to 2–3 mm, resulting in controlled tissue trauma and reduced risk of perforation or bleeding[100]. This technique may be of future use in FAP.

Sulindac. Both retrospective and prospective clinical studies have suggested that non-steroidal anti-inflammatory drugs (NSAIDs) may protect against gastrointestinal cancer[101–103], an observation also made in animal studies[104]; the exact mechanism of action is unknown. NSAIDs inhibit cyclo-oxygenase (COX) which converts arachidonic acid to prostaglandins, thromboxanes and prostacyclins. These prostaglandins may affect cell proliferation and tumour growth through activation of second messenger systems, as they have been found in significant quantities in several cancers, including adenocarcinomas[105]. NSAIDs have also been shown to inhibit cell proliferation, presumably through their inhibitory affect on COX.

There are two COX enzymes in humans, COX-1 and COX-2. Animal studies in mice with mutations in the *Apc* gene showed that polyp regression occurred when COX-2 activity was suppressed, providing direct evidence that COX-2 plays a key role in tumorigenesis in an FAP animal model[106]. Most NSAIDs suppress both COX-1 and COX-2 activity and, although not specific in their action, appear to have an inhibitory effect on tumour development. Gastrointestinal side-effects caused by NSAIDS seem to be mediated through COX-1 inhibition, so there may be clinical value in the development of selective COX-2 inhibitors.

The first report that the NSAID sulindac might affect rectal adenomas in FAP was in 1983[107]. Since then several trials have shown benefits when using sulindac to control not only rectal[108,109] and duodenal[110], but also desmoid[111], disease. A randomized controlled trial of the effect of sulindac on duodenal polyps showed regression of early adenomas[112], but there was no reduction in the size of larger adenomas[110], perhaps as the latter had further genetic change, such as *TP53* mutation[68], which might have made them unresponsive. Indices of cell proliferation were also reduced[110,113]. Others have found in the rectum that reduction in polyp size is only partial and depends on the length of treatment[114], and that withdrawing the drug results in recurrence of the adenomas[109]. However Winde *et al.*[108], using sulindac suppositories, have claimed complete and long-term suppression with a low dose of 67 mg/day. Whatever the reality, it seems that large polyps are relatively unresponsive and cancer still occurs in patients with polyp regression[115,116].

Sulindac is the only medication so far which has shown any measurable effect on duodenal polyposis. Drugs such as calcium[117], vitamin C[118] or starch[119] have been evaluated in patients with FAP, but they have had no demonstrable effect on duodenal disease[120]. There are several clinical trials currently under way examining the effects of various modified NSAIDs in the duodenum of patients with FAP.

Antacids. The observation that DNA adducts form at a more acid pH raises the question as to whether some form of acid lowering therapy might influence duodenal disease in FAP. One randomized placebo controlled trial is currently under way and should answer this question.

Conclusion

Surgeons treat the large bowel component in polyposis either by colectomy and ileorectal anastomosis or by restorative proctocolectomy. Thereafter, upper gastrointestinal disease becomes an increasingly important problem in patient management. For large bowel disease there is a virtual 100 per cent risk of cancer if left untreated, but for upper gastrointestinal disease only about 5 per cent of patients will develop cancer, despite 90 per cent or more having adenomas.

As the best management of upper gastrointestinal disease is not yet known, frequent surveillance seems inappropriate. Currently at St Mark's Hospital endoscopy is commenced at age 25 years, with lesser degrees of polyposis being screened at intervals of 5 years. For more advanced disease, the screening frequency is increased, sometimes to intervals of 6 months. When confronted by a case of advanced duodenal polyposis the choice lies between continued surveillance or surgical clearance; there are substantial problems with either decision.

The long-term answer surely lies with some form of drug therapy. At the moment modified NSAIDs and antacids are being tried, but in the future gene therapy[121] may have a place, particularly if a delivery system via the biliary tree is devised. Port access through the gallbladder would allow liposomes containing normal *APC* to transfect cells mucosally exposed to bile, thus targeting the exact distribution of upper gastrointestinal adenomas.

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Results of pancreatogastrostomy after pancreatoduodenectomy in 160 consecutive patients

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Background The advantages of pancreatogastrostomy over pancreatojejunostomy after pancreaticoduodenectomy are still debated. This study analyses the results of pancreatogastrostomy to identify factors that could influence immediate outcome.

Methods During a 10-year period, 160 consecutive patients underwent a pancreatogastrostomy. There were 109 men (68 per cent) and 51 women (32 per cent) with a mean(s.d.) age of 59(10) (range 22–82) years; 27 patients were older than 70 years. The following parameters were assessed: mortality rate, morbidity, reasons for reoperation, length of hospital stay, duration of nasogastric tube and drainage.

Results Hospital mortality rate was 3 per cent; overall morbidity rate was 30 per cent. The reoperation rate was 12 per cent, mainly because of bleeding at the pancreatic margin. Delayed gastric emptying occurred in 36 patients. The overall rate of pancreatic fistula was 2·5 per cent. Age, sex, indications for pancreatoduodenectomy, and the texture of the pancreatic remnant did not influence the occurrence of pancreatic fistula or delayed gastric emptying.

Conclusion This study confirmed that pancreatogastrostomy is a safe procedure with low mortality and morbidity rates.

Since 1990, several authors have reported a postoperative mortality rate of less than 8 per cent after pancreatoduodenectomy, and some have achieved nil mortality[1–9]. Surgical experience, patient selection and the decrease of postoperative morbidity undoubtedly represent the main factors explaining this dramatic reduction[1–4]. Given that morbidity is often related to the occurrence of pancreatic fistula[10], it is essential to work towards the reduction of this risk.

Recently published studies[11–19] have emphasized the advantages of pancreatogastrostomy although firm conclusions cannot be drawn because of the retrospective nature of the studies and/or an insufficient number of patients.

In the present study the results of pancreatogastrostomy were collected prospectively for 160 consecutive patients during a 10-year period and assessed to identify factors that could influence immediate outcome.

Patients and methods

A total of 160 consecutive patients underwent pancreatogastrostomy after pancreaticoduodenectomy between 1987 and 1996. There were 109 men (68 per cent) and 51 women (32 per cent) with a mean(s.d.) age of 59(10) (range 22–82) years; 27 patients were older than 70 years. The indications for operation are listed in *Table 1*.

After resection, a hand-sewn pancreatogastrostomy was carried out through a posterior gastrostomy with one layer of interrupted sutures (3/0 polyglactin). When the pancreatic duct was not dilated it was stented to avoid occlusion.

Oral intake was permitted the day after removal of the nasogastric tube. Drains were removed progressively according to the amount of fluid recovered. A pancreatic fistula was defined as the recovery of more than 50 ml of amylase-rich fluid (more than five times the normal plasma levels) from the drain site during the postoperative period. The fistula track was confirmed radiologically with water-soluble contrast agents. Delayed gastric emptying was defined as the presence of a nasogastric tube more than 10 days after surgery, or its reinsertion because of vomiting.

Statistical analysis

All data were collected prospectively. The following parameters were assessed: mortality, morbidity, reasons for reoperation, length of hospital stay, duration of nasogastric tube and drainage.

Student's *t* test and χ^2 test were used for statistical analysis. A univariate analysis was carried out to compare patients with and without delayed gastric emptying and/or pancreatic fistula.

Results

Pathological examination of the pancreatic resection margin was negative in 127 patients (79 per cent), showed

Table 1 Indications for pancreaticoduodenectomy

	n
Pancreatic duct cancer	69 (43)
Cancer of the ampulla	24 (15)
Chronic pancreatitis	21 (13)
Distal bile duct cancer	13 (8)
Mucinous ductal ectasia	5 (3)
Serous cystadenoma	5 (3)
Mucinous cystadenoma	3 (2)
Pseudocyst of the pancreas	3 (2)
Duodenal adenocarcinoma	3 (2)
Islet cell tumour	2 (1)
Pancreatic trauma	2 (1)
Miscellaneous	10 (6)
Total	160 (100)

Values in parentheses are percentages

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chronic pancreatitis in 25 (16 per cent) and tumour foci in eight (5 per cent). The texture of the pancreas remnant was considered normal in 113 patients (71 per cent) and fibrotic in 47 (29 per cent).

The hospital mortality rate was 3 per cent ($n = 5$). Causes of death were multiple organ failure ($n = 2$), myocardial infarction ($n = 1$), sepsis ($n = 1$) and pneumonia ($n = 1$). The overall morbidity rate was 31 per cent ($n = 49$). Complications requiring reoperation in 19 patients (12 per cent) included: haemorrhage at the pancreatic margin ($n = 7$), wound dehiscence ($n = 3$), pancreatic fistula ($n = 2$), haemoperitoneum ($n = 2$), intestinal obstruction ($n = 1$), thrombosis of the mesenteric vein ($n = 1$), biliary leak ($n = 1$), necrosis of the pancreatic remnant ($n = 1$) and wound infection ($n = 1$).

Complications managed conservatively in 30 patients (19 per cent) included: delayed gastric emptying ($n = 20$), fistula at the gastrojejunostomy ($n = 3$), pancreatic fistula ($n = 2$), intra-abdominal abscess ($n = 10$), bile leak ($n = 1$), pneumonia ($n = 1$), liver abscess ($n = 1$) and wound infection ($n = 1$).

The overall rate of delayed gastric emptying was 22 per cent ($n = 36$). Thirteen patients had a nasogastric tube in place for more than 10 days and nine patients for more than 20 days.

Univariate analysis showed that patients with or without delayed gastric emptying were similar in age, sex, indications for pancreaticoduodenectomy and texture of the pancreatic remnant. The reoperation rate was significantly higher ($P < 0{\cdot}0001$) and the mean hospital stay longer ($P < 0{\cdot}0001$) in patients with delayed gastric emptying than those without.

The overall rate of pancreatic fistula was 2 per cent ($n = 4$). The comparison of patients with pancreatic fistula *versus* those without pancreatic fistula failed to reveal significant predictors. Mean length of hospital stay was 10 days longer in patients with pancreatic fistula ($P < 0{\cdot}02$).

Mean(s.d.) length of hospital stay was 22 (9) days. The mean duration of abdominal drainage was 8 (range 0–37) days.

Discussion

Pancreatic fistula following pancreaticoduodenectomy has been considered a serious event with a frequency varying from 10 to 30 per cent. Moreover, it has been a life-threatening condition responsible for death in one-half or one-third of patients[10]. Consequently, many technical variations have been described to improve quality and safety of the pancreatic anastomosis, either with new techniques of pancreatojejunostomy[20–22], by reinforced anastomosis with fibrin glue sealing[23], the avoidance of the anastomosis with occlusion of the pancreatic duct[24,25], the use of octreotide to reduce pancreatic secretion[26,27], or with the achievement of a pancreatogastrostomy. The feasibility of the latter has been demonstrated in experimental studies[28] and humans[29].

Considering the literature of the past 5 years, the authors noted that the rate of pancreatic fistula remained stable, but related fatal complications have decreased significantly (*Table 2*). In the same period a few single institutional reports underlined the safety of pancreatogastrostomy (*Table 3*) and some reported no pancreatic fistula[12,14,17,19]. Although these encouraging results should be evaluated in the light of selection bias (retrospective analyses and limited numbers of patients), a new impetus was offered to this old surgical technique.

The authors began using pancreatogastrostomy in 1987. It then became the standard procedure in the department for all patients referred for pancreaticoduodenectomy whatever the indications for operation, age and status of the patient, texture of the remnant pancreas and intra-operative difficulties encountered. This operation was always carried out by senior surgeons experienced in pancreatic surgery.

Some technical details are noteworthy: (1) the left pancreas must be freed from the splenic vein to allow it to lie upright without strain towards the posterior gastric wall; (2) perfect haemostasis of the pancreatic remnant is essential; (3) the insertion of the pancreas stump through a short gastrostomy secured with one layer of absorbable interrupted stitches; and (4) insertion of a thin catheter in a non-dilated pancreatic duct to prevent it being closed during the anastomosis. Following these rules, the edge of the pancreatic stump must protrude in the gastric lumen by 2–3 cm, which is easily checked during gastro-enterostomy.

In the present study the hospital mortality rate was 3 per cent which compared favourably with that of a comprehensive review of the literature (*Table 3*). Moreover, it is also comparable to that reported in recent series including more than 100 pancreatoduodenectomies with a

Table 2 Results of Whipple resection from series including more than 100 patients and published since 1990

Reference	Year	No. of patients	Mortality rate (%)	Morbidity rate (%)	Pancreatic fistula rate (%)	Delayed gastric emptying rate (%)	Relapse rate (%)
Trede *et al.*[9]	1990	107	0		7		6
Miedema *et al.*[7]	1992	279	3·6	46			
Matsumoto *et al.*[8]	1992	100	6	27	16		
Cameron *et al.*[1]*	1993	145	0	36	19	32	1
Edge *et al.*[6]	1993	168	6	24 major 19 minor			
Baumel *et al.*[5]	1994	555	8	34			
Yeo *et al.*[34]	1995	145		46	11·7	22	
Fernandez del Castillo *et al.*[2]	1995	142	0	43	6·3	11·2	1·4
Wade *et al.*[3]	1995	369	8	37	5		

*Including nine total pancreatectomies

Table 3 Results of pancreatogastrostomy after pancreaticoduodenectomy: comprehensive review

Reference	Year	*n*	Pancreatic fistula (*n*)	Haemorrhage (*n*)	Mortality (*n*)
Mackie *et al.*[31]	1975	25	1		2
Eggert and Teichmann[32]	1982	11	1		1
Telford and Mason[20]	1984	5	0		
Flautner *et al.*[16]	1985	27	0	1*	0
Kapur[17]	1986	31	0	2 (1*)	2
Reding[33]	1988	49	1		
Icard and Dubois[15]	1988	17	0	1*	
Ramesh and Thomas[37]	1990	13	0		
Delcore *et al.*[14]	1990	45	0	1 (1*)	1
Adloff *et al.*[36]	1992	15	2	2	1
Sauvanet *et al.*[13]	1992	32	1 (1*)	1	1
Miyagawa *et al.*[38]	1992	21	1		
Morris and Ford[12]	1993	8	0		
Arnaud *et al.*[18]	1993	32	1*		2
Takao *et al.*[30]	1993	46	1		2
Yeo *et al.*[34]	1995	73	9		
Mason and Freeark[19]	1995	34	0	1	3
Andivot *et al.*[35]	1996	16	2 (1*)	1 (1*)	2
Pilarsky *et al.*[39]	1997	28	4	3 (3*)	1
Present series	1998	160	4 (2*)	7*	5
Total		688	28 (4%)	20 (3%)	23 (3%)

*Patient reoperated for complication.

majority of pancreatojejunostomy (*Table 2*). Thus, pancreatogastrostomy did not impair the expected results of pancreatoduodenectomy.

The reoperation rate was 12 per cent (19 of 160). The major cause of reoperation was upper gastrointestinal haemorrhage (seven of 19); the diagnosis is evident and prompt reoperation is often required. This particular complication represents 3 per cent of patients in the review. Trede *et al.*[9] reported such complications in 4 patients after 118 consecutive pancreatoduodenectomies (107 Whipple and 11 total resections). However, in these cases haemorrhage was mostly located at the gastroenterostomy and not on the site of the pancreatojejunostomy. In the experience of the authors haemorrhage was often related to small bleeding arteries located on the pancreatic edge. Whether pancreatogastrostomy increases the risk of postoperative digestive haemorrhage is questionable. It could be hypothesized that the gastric lumen is larger than the jejunal lumen and does not favour spontaneous clotting. Consequently, perfect haemostasis of the pancreatic stump is required, preferably with stitches rather than electrocoagulation and should be checked from inside the stomach during the gastroenterostomy. Other authors[13] have also attached importance to rigorous haemostasis of the gastric submucosa. During reoperation bleeding was always easy to control with stitches applied to the pancreatic surface through an anterior gastrotomy.

Postoperative pancreatic fistula was a rare event in the study but two required reoperation. This low rate of pancreatic fistula (2 per cent) compares favourably with those of the comprehensive review. No death was related to pancreatic fistula, but hospital stay was significantly longer.

Other studies[7,8] have highlighted numerous factors as determinant parameters of pancreatic fistula. Texture of the remnant pancreas, size of the pancreatic duct and the surgeon's experience were reported as the most significant parameters[34,35].

In retrospective comparative studies between pancreatojejunostomy and pancreatogastrostomy the results concerning the risk of pancreatic fistula are conflicting[35,38]. Some authors have pointed to the safety of pancreatogastrostomy lessening the number of pancreatic fistulas[19,37,38]; others have denied this assertion[8]. In a recent prospective randomized study the occurrence of pancreatic fistula was not significantly influenced by the type of anastomosis[34].

In fact the most problematic postoperative complication noted in this study was delayed gastric emptying (22 per cent). The rate of this complication following pancreaticoduodenectomy ranges from 20 to 50 per cent, particularly after pylorus-preserving procedures[1,2]. The majority of patients in this study underwent partial gastrectomy rather than a pylorus-preserving operation and no difference was noted between the two techniques. The cause is unknown and can occur in the absence of medical or surgical complications as noted in two-thirds of the present patients complaining of delayed gastric emptying. To the authors' knowledge there is no published study evaluating the role of the pancreatogastrostomy on gastric motor function. In their comparative study Yeo *et al.*[34] reported a comparable rate of delayed gastric emptying (22 per cent) after either pancreatojejunostomy or pancreatogastrostomy. Long-term functional outcome of pancreatogastrostomy after pancreatoduodenectomy is rarely evaluated because this procedure is often proposed for patients with pancreatic malignancy. Theoretically the lack of enterokinase in the gastric mucosa prevents the activation of pancreatic enzymes lessening the risk of pancreatic duct stenosis[39]. Pain and Knight[40] noted a higher incidence of steatorrhoea in patients undergoing pancreaticogastrostomy for duct drainage chronic pancreatitis. Johnson[41] demonstrated the presence of pancreatic enzymes in response to hormones and normal gastric secretion many years after operation.

In conclusion this study confirmed that pancreatogastrostomy is a safe procedure with low mortality and morbidity rates. Further prospective randomized studies are required to clearly define whether pancreatogastrostomy is a real improvement or a fashionable procedure. Undoubtedly these studies should be reserved for specialized centres that have carried out a large volume of pancreatic resections, have experienced surgeons, and where the mortality and pancreatic fistula rates are less than 5 per cent.

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Percutaneous aspiration for bacteriological studies in patients with necrotizing pancreatitis

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Background Percutaneous computed tomography (CT)-guided aspiration of abdominal collections is performed in necrotizing pancreatitis to detect infection of necrosis, which is an adverse prognostic factor and requires surgical drainage. However, in the case of sterile aspirates, the outcome and the optimum management are subject to debate. This study examined the clinical and bacteriological outcome of patients with severe acute pancreatitis with initially sterile necrosis and assessed the efficiency of percutaneous drainage in this setting.

Methods Seventeen patients hospitalized for necrotizing pancreatitis with a septic course underwent a preliminary sterile CT-guided aspiration. Eight patients underwent simultaneous percutaneous drainage of the punctured collection. Supportive therapy was continued unless severe clinical deterioration or proven secondary infection of necrosis indicated the need for necrosectomy and drainage.

Results Secondary infection of necrosis was observed in two patients of nine who had only fine-needle aspiration cytology of the collection, and in seven of eight it was drained percutaneously ($P = 0 \cdot 01$). Only one patient drained percutaneously recovered without surgery. Surgical drainage was required in 12 patients. The hospital mortality rate was 29 per cent and was not significantly affected by the bacteriological status of necrosis.

Conclusion Percutaneous drainage of sterile collections predisposed to secondary infection of the necrosis and did not cure the patients. A first sterile percutaneous aspiration did not predict a favourable course and surgery frequently remains necessary.

Despite improvements in intensive care management, imaging techniques, and surgical strategies, the mortality rate of necrotizing pancreatitis is still 8–35 per cent[1,2]. Since the work of Beger *et al.*[3], infection of necrotic pancreatic and peripancreatic tissues has been widely recognized as a strong adverse prognostic factor. Infection of necrosis complicates the course of about 30 per cent of necrotizing pancreatitis[4], and can be now diagnosed by percutaneous computed tomography (CT)-guided aspiration[5,6].

There is general agreement that infected pancreatic necrosis is an absolute indication for surgical drainage[6–8]. Pancreatic abscesses and fluid collections associated with necrosis can be drained percutaneously[9,10]. In contrast, the evolution and management of sterile necrosis remain controversial[11]. Overall mortality has been reported in sterile necrosis to be 0–36 per cent[1,7,12], and some authors advocate surgical abstention[7], whereas others favour drainage of symptomatic collections, irrespective of their bacteriological status[13].

To assess the bacteriological and clinical evolution of patients presenting with initially sterile necrosis and the efficiency of percutaneous drainage of sterile collections, the records of patients admitted for necrotizing pancreatitis with a sterile CT-guided percutaneous aspiration were studied.

Patients and methods

Between June 1985 and May 1995, 269 patients with acute pancreatitis were admitted. According to the clinical course, CT scans and operative reports, 71 patients were considered to have necrotizing pancreatitis and were treated in an intensive care unit. Because of clinical suspicion of infected necrosis, based on temperature of over 38·5°C and leucocytosis of more than 10 000 per mm^3, unexplained by another source of sepsis, 48 patients underwent an initial CT-guided percutaneous aspiration of intra-abdominal collection or mass to provide samples for bacteriological analysis. In 31 patients, bacteria were found in the aspirated material. In this group of patients 27 were operated on: 19 had infected necrosis, six had pancreatic abscess and two had sterile necrosis. In the four remaining patients, pancreatic abscesses were drained percutaneously and no operation was required. The mortality rate in this group was 12 of 31. In 17 patients the material collected from percutaneous aspiration was sterile.

The remaining 23 patients who had no percutaneous drainage or puncture had a complicated course. Two patients died before operation on day 3 after onset of pancreatitis. The other patients were operated on: 13 had infected pancreatic necrosis, four had sterile necrosis, four had a pancreatic abscess. Sixteen of the 23 patients were referred from other centres and 12 had been operated on. The mortality rate in this group was nine of 23. In this group of patients percutaneous aspiration was not performed either because the diagnosis of infected necrosis was already made or because percutaneous aspiration was judged technically difficult or dangerous.

Computed tomography

Contrast-enhanced CT scans were taken to delineate extrapancreatic collections and necrosis of the pancreas itself (necrosis was suspected when there were non-enhanced areas of less than 40 Hounsfield units[7], and was classified by the radiologist as absent or affecting less or more than 50 per cent of the gland). All CT scans were graded according to Balthazar's classification[14]. Only collections with safe percutaneous access were aspirated. A part of the fluid aspirated was Gram stained

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and immediately analysed by the bacteriologist, whereas the remainder was cultured for aerobic or anaerobic bacteria and fungus. At the beginning of the authors' experience, without waiting for the results of bacteriological examination, a single-lumen pigtail drain (14-Fr) was inserted frequently in the fluid collections after dilatation of the needle track, and left in place for prolonged drainage.

Study group

In 17 patients the first percutaneous aspiration provided sterile material, in eight of whom a pigtail catheter was left in the collection. Only bacteriologically proven infection of non-drained necrosis or severe clinical deterioration with a septic state uncontrolled by supportive treatment prompted surgical drainage with necrosectomy.

The clinical, biological, bacteriological and radiological data of the 17 patients who initially had sterile necrosis, were collected prospectively and constituted the basis of this study. There were 11 men and six women with a median age of 53 (range 41–71) years. The cause of pancreatitis in nine patients was alcohol abuse, biliary lithiasis in six patients, endoscopic spincterotomy in one and unknown in one. The median Ranson[15] score was 4 (range 2–8). Patients were hospitalized with a median delay of 6 (range 0–23) days after the onset of symptoms.

The clinical status of the patients in the 24 h preceding the percutaneous aspiration was assessed by the Simplified Acute Physiology Score (SAPS) which evaluates the risk of death in patients in the intensive care unit[16]. Bacteriological examination of iterative percutaneous CT-guided aspiration, fluids drained by percutaneous pigtail drains, and fluids or necrosis yielded peroperatively were recorded.

Statistical analysis

Statistical analysis was performed using Fisher's exact test (two-tail). $P < 0{\cdot}05$ was considered significant. Values are expressed as mean(s.d.) or median(range).

Results

Clinical status and biochemical parameters preceding percutaneous aspiration

CT-guided percutaneous aspirations were performed a mean(s.d.) of 16(7) days after the onset of pancreatitis. Mean(s.d.) SAPS was 8·6(2·4) (expected mortality rate 20 per cent). Abdominal guarding and ileus were noted in one-half of the patients and encephalopathy was observed in a single patient. Hypocalcaemia was noted in six patients. Serum amylase concentration showed a wide range of values (22–2127 units/l), and was still raised (over 100 units/l) in 13 patients.

CT scan and percutaneous aspiration

All patients had a grade E (2–6 fluid collections) contrast-enhanced CT scan. A non-enhanced pancreatic area involved less than one-half of the gland in nine patients and more in five. Three patients had only peripancreatic collections and necrosis was proven later by surgery or autopsy. A pleural effusion was present in ten patients. Aspirated collections were located in the lesser sac in 11 patients and in the left pararenal anterior space in six. These locations were encountered most frequently (*Table 1*) and were frequently associated with a third collection located in the mesentery, which was not punctured because of vascular risk. A pigtail drain was left in place in eight patients. During the hospital course, seven patients underwent a second percutaneous aspiration of the same collection and two of them had a third aspiration of the same persisting collection. Among the eight patients treated by percutaneous drainage of initially sterile collections, two patients had a second percutaneous drain insertion and one patient underwent a third percutaneous drainage.

Bacteriological findings

Five patients had received antibiotics intravenously for more than 24 h when the first percutaneous aspiration was performed.

Nine patients developed a secondary infection of necrosis during their hospital stay (*Table 2*). Secondary infection was proven by peroperative bacteriological sampling in case of surgical drainage or, if the patient was not operated on, by bacteriological analysis of the material harvested by iterative percutaneous aspiration or drain. Secondary infection was observed in two of nine patients who had only fine-needle aspiration cytology (FNAC) of the sterile collection *versus* seven of eight patients who underwent percutaneous drain insertion ($P = 0{\cdot}01$) (*Table 2*). Secondary infections were diagnosed after a median delay of 15 (range 2–53) days after the initial sterile percutaneous aspiration (*Fig. 1*). Bacteria encountered are listed in *Table 3*.

Treatment and outcome

Of the nine patients treated without percutaneous drainage two were treated without surgery; one recovered and one died from sudden irreversible multiple organ failure (MOF) without bacteriologically proven sepsis.

Table 1 Location of intra-abdominal extrapancreatic collections on computed tomographic scans

Location of collection	No. of patients
Lesser sac	17
Left anterior pararenal space	14
Mesentery	12
Transverse mesocolon	3
Left posterior pararenal space	2
Right anterior pararenal space	2
Right posterior pararenal space	1
Pelvis	1

Two of six collections per patient were observed on computed tomographic scan

Table 2 Micro-organisms found in the necrotic collections by percutaneous aspiration, percutaneous drainage or surgical sampling

Gram stain	Micro-organism	No. of patients
Gram-negative	*Pseudomonas aeruginosa*	3
	Klebsiella oxytoca	2
	Escherichia coli	1
	Hemophilus	1
	Morganella	1
	Aerobacter	1
Gram-positive	*Staphylococcus* coagulase$^-$	2
	Staphylococcus coagulase$^+$	1
	Streptococcus	1

Nine patients ultimately had infected necrosis. In four, two different bacteria were identified by the bacteriological analysis

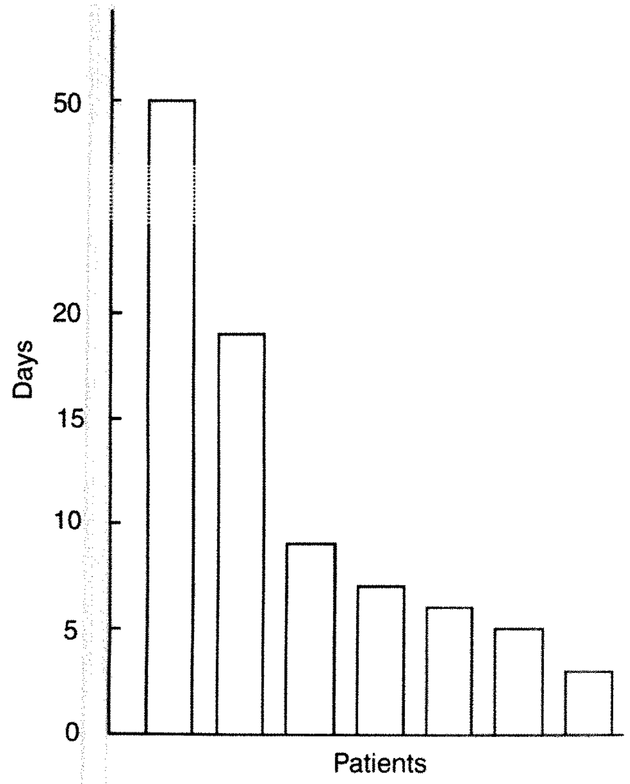

Fig. 1 Delay from drain placement to infection occurrence

Table 3 Treatment and outcome in 17 patients with a first sterile percutaneous aspiration of pancreatic or peripancreatic collection

CT-guided procedure	Final treatment	Bacteriological outcome	In-hospital mortality
Aspiration ($n = 9$)	No surgery ($n = 2$)	Sterile ($n = 2$)	1
	Surgery ($n = 7$)	Sterile ($n = 5$)	1
		Infected ($n = 2$)	1
Drainage ($n = 8$)	No surgery ($n = 3$)	Infected ($n = 3$)	1
	Surgery ($n = 5$)	Sterile ($n = 1$)	0
		Infected ($n = 4$)	1

Bacteriological outcome was defined by: (1) bacteriological results of the analysis of the last aspiration performed or the analysis of the fluids drained by a percutaneously inserted pigtail drain if the patient was not operated; (2) bacteriological analysis of the samples harvested during operation if the patient underwent surgical drainage and necrosectomy. CT, computed tomography

Seven patients ultimately required surgical drainage and necrosectomy.

Among the eight patients treated initially with percutaneous drainage two recovered despite a secondary infection of the drained collection (one without sequelae and one with a late pseudocyst treated by surgical cystogastrostomy), one patient died from septic shock 48 h after the percutaneous drainage with a secondary staphylococcal infection of the initially sterile drained collection, and five patients ultimately required surgical drainage and necrosectomy.

Thus, in the whole series, two patients died among the five who were not operated on and 12 patients ultimately underwent surgical drainage and necrosectomy. Operation was performed after a median delay from the initial aspiration of 14 (range 3–53) days (*Fig. 1*). The indications for surgical treatment are detailed in *Table 4*. Before operation, infection of necrosis was proven or only suspected because of Gram-negative bacteria in blood cultures from five patients, and was confirmed during operation in four. Among seven patients without preoperative proof of infection, necrosis found during operation was sterile in five patients and infected in two. Three patients died after surgery, two from sepsis and one from pulmonary embolism accounting for a surgical mortality rate of 25 per cent. Eight patients required several surgical procedures (range 2–4) during their initial stay and later readmissions to treat biliary lithiasis, pseudocyst or fascial disruption.

Table 4 Indications for surgical drainage

Status before operation	No. of patients	Proven infection of necrosis
Sepsis syndrome and positive percutaneous aspiration	3	2
Sepsis syndrome and positive percutaneous drainage	1	1
Sepsis syndrome and positive blood culture	1	1
Sepsis syndrome and gastrointestinal tract haemorrhage	3	1
Sepsis syndrome and one or more altered vital function	4	1

Sepsis syndrome was defined by the conjunction of fever over 38·5°C, white blood cells of more than 10 000 and, in some cases, a septic haemodynamic profile. Infection of necrosis was proven by peroperative bacteriological sampling systematically collected

The mortality rate of 25 per cent (two of 18) in the group of patients initially drained percutaneously did not differ significantly from the 33 per cent (three of nine) mortality rate observed in the group of patients treated without percutaneous drain insertion. Among the eight patients with sterile necrosis, two died. Among the nine patients with secondarily infected necrosis, three died. The mean stay in intensive care unit for survivors was 63 (range 23–114) days.

Discussion

In this series, percutaneous aspiration was always performed in severe pancreatitis as recommended by Gerzof *et al.*[6]. The median Ranson score was high, and the bioclinical status of the patients during the 24 h preceding the aspiration assessed by the SAPS indicated an expected mortality rate of 20 per cent. The severity of the pancreatitis was also demonstrated by CT scans showing grade E lesions in all patients[14] and the presence on CT scan of non-enhanced pancreatic areas[7,17] in 13. The 35 per cent rate of first sterile aspiration (17 of 48) observed in patients is comparable to the 40 per cent rate reported by Gerzof *et al.*[6].

The severity of the initial bioclinical status accounts for the length of hospital stay and the overall mortality rate of 29 per cent observed in this series of initially sterile necrotic pancreatitis. Karimgani *et al.*[12] recently reported

26 patients whose necrosis remained sterile throughout their hospital course with a mortality rate of 38 per cent.

Prolonged percutaneous drainage of initially sterile collections led to secondary infection of drained collections in seven of eight patients confirming recently published data[18]. Nevertheless, percutaneous drainage did not significantly increase mortality, compared with patients without percutaneous drain insertion. Among the eight patients drained percutaneously, only two recovered without surgical necrosectomy and one of them developed a late pseudocyst requiring surgical cystogastrostomy. This observed failure of percutaneous drainage and the infection rate prompted the abandonment of this therapeutic modality in patients with sterile collections, as done previously in case of pancreatic abscess[8]. The current policy is to perform percutaneous aspiration during the first CT examination in order not to overlook a pancreatic infection. If the bacteriological cultures are sterile medical supportive treatment is continued. CT scans are performed every week with routine aspiration, or sooner when a clinical event (organ failure, increased white cell count) suggests pancreatic infection. When bacteria are found patients undergo operation.

Despite a policy of initial conservative treatment of sterile necrotizing pancreatitis, 12 of 17 patients underwent operation during hospital stay because of infection of necrosis or because of severe bioclinical deterioration. These results differ markedly from those of Bradley and Allen[19] who reported a series of 11 patients with sterile necrosis, all successfully treated without surgery. However, their patients had less extended pancreatic necrosis involving a mean(s.d.) of 38(4) per cent of the gland, and five of them did not undergo CT-guided percutaneous aspiration because they had a straightforward clinical course. The present results differ also from the series of 50 sterile aspirations reported by Gerzof *et al.*[6] in which necrosis remained sterile in all cases, compared with secondary infection which occurred in nine of the present patients, two of whom did not undergo percutaneous drainage. After a first sterile aspiration, secondary infection of pancreatic necrosis can be explained, either because the first puncture was performed before subsequent infection, or by the coexistence of separate sterile and infected collections in the same patient accounting for a false-negative rate of FNAC of 10 per cent[13,20]. The use of antibiotics causing high pancreatic tissue concentration[21] may also impair bacteriological analysis.

The 29 per cent overall mortality rate observed in this series of initially sterile necrosis was comparable to the mortality rates reported for infected necrosis[2,3,13,22,23]. Furthermore, the patients secondarily infected in this series did not have a worse prognosis than the patients whose necrosis remained sterile, as recently reported by Rattner *et al.*[13]. This questions the true role of infection of necrosis commonly considered to be a strong adverse prognostic factor[3,24]. This study was not multivariate, but analysis reveals that the extent of pancreatic and extrapancreatic necrosis was a prognostic factor as strong as infection. Beger *et al.*[3] noticed that infection was favoured by the extent of necrosis, as has been recently demonstrated in experimental pancreatitis in a rodent model of graded severity[25]. Finally, it is noteworthy that antibiotic prophylaxis of infection of necrosis, provided either by intravenous broad spectrum antibiotics[26] or by selective intestinal decontamination[27] effectively reduced infection rates in large controlled studies, but did not reduce mortality. Infection may therefore be indirect evidence for extensive necrosis, which would be the main independent prognostic factor.

As no case of infected necrosis cured by antibiotics and supportive therapy has been reported, percutaneous aspiration of the collections seen at CT is justified, a septic aspirate indicating the need for surgical drainage. When the first percutaneous aspiration performed for severe necrotizing pancreatitis is sterile, the subsequent course is not necessarily favourable. Patients with sterile necrosis may recover with supportive treatment, but one-half of the patients suffer secondary infection of necrosis, this being favoured by percutaneous drainage which should be therefore avoided. Repeated percutaneous aspirations should be performed if the condition of the patient deteriorates. Surgical necrosectomy and drainage appeared to be ultimately frequently required because of bioclinical deterioration, even if infection of necrosis was not demonstrated by repeated percutaneous aspiration.

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Co-existing biliary anomalies and anatomical variants in choledochal cyst

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Background Excision is the treatment of choice for choledochal cyst, and free bile drainage is essential to avoid ascending cholangitis. However, anastomosis between the relatively narrow common hepatic duct and bowel (conventional anastomosis) in case of type IV-A cyst, co-existing biliary anomalies and anatomical variations may cause ascending cholangitis resulting from insufficient biliary decompression.

Methods One hundred and four patients with choledochal cyst were treated by cyst excision. Conventional anastomosis was performed in 22 patients and hilar anastomosis in 82.

Results An anastomotic stricture developed in nine of the 22 conventional anastomosis cases and all required reoperation. Of the 82 hilar anastomosis cases, only one required reoperation for a primary stricture. Co-existing biliary anomalies and anatomical variants were seen in 26 patients: (1) primary stricture in 18; (2) aberrant posterior duct in two; (3) low confluence of the hepatic ducts in two; (4) aberrant hepatic artery in two; and (5) very small bile duct in two. All 26 patients underwent widening of the ductal lumen (ductoplasty) or additional procedures.

Conclusion Complete removal of the extrahepatic bile duct and a wide hilar anastomosis is essential to prevent ascending cholangitis. Ductoplasty or additional procedure can be performed only at the hilum.

Excision has long been the treatment of choice for choledochal cyst with pancreatobiliary malunion[1]. Although Roux-en-Y hepaticojejunostomy distal to the hilum has been employed widely and conventionally for the subsequent biliary–enteric anastomosis, it does not protect against recurrent cholangitis if anastomotic or primary intrahepatic ductal strictures are present[2]. Free bile drainage is essential to avoid ascending cholangitis and can be obtained by a wide anastomosis at the hepatic hilum[3,4]. Anastomosis between the common hepatic duct and bowel (conventional anastomosis) performed in a type IV-A cyst often produces a relatively small anastomosis, as compared with intrahepatic ductal dilatation, and may result in insufficient biliary decompression[4]. In addition, co-existing biliary anomalies or anatomical variations are observed occasionally around the hepatic hilum[5,6] and require additional procedures to ensure free bile drainage in biliary reconstruction. The purpose of this paper is to advocate hilar hepaticoenterostomy for preventing ascending cholangitis and to describe surgical correction of these anomalies and variations.

Patients and methods

Between March 1969 and March 1997, 104 patients with choledochal cyst were treated by excision (cyst removal and biliary reconstruction) (*Fig. 1*). The first 22 patients before 1976 underwent a hepaticoenterostomy distal to the hilum (conventional anastomosis), nine of whom required reoperation for ascending cholangitis resulting from anastomotic stricture which developed several years after initial surgery. The nine patients presented either with a type I cyst (three patients) or type IV-A cyst (six), and underwent duodenostomy (four) or Roux-en-Y jejunostomy (five)[4].

In 1976, reoperation was required for anastomotic stricture in a young female patient who had undergone cyst excision and conventional anastomosis 7 years previously[2], and the choice of conventional procedure was re-evaluated. Subsequently, the 82 patients since 1976 have undergone hepaticoenterostomy at the hepatic hilum to provide a wider stoma, regardless of intrahepatic involvement[7].

Additionally, associated biliary malformations including primary ductal stricture and anatomical variations, which were corrected by some additional procedure at the time of biliary reconstruction, have also been recorded.

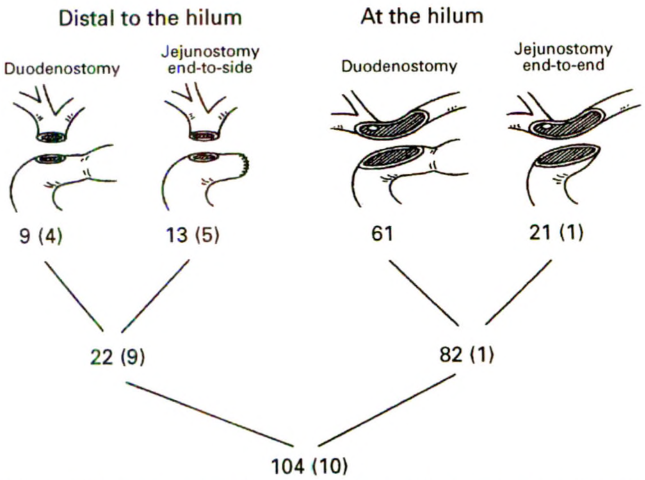

Fig. 1 Biliary reconstruction after cyst excision performed in 104 patients between March 1969 to March 1997. Numbers in parentheses indicate the number of patients who underwent reoperation

Paper accepted 20 October 1997

Results

There were no operative deaths. All patients were asymptomatic except for the nine with anastomotic stricture after conventional anastomosis[4] and one with primary simple ductal stricture described below. Of 104 patients, 55 (52·9 per cent) presented with a type IV-A cyst with an intrahepatic component, and 26 (25·0 per cent) had co-existing biliary anomalies and anatomical variations (*Table 1*; *Fig. 2*).

Primary ductal stricture

Primary ductal stricture was observed in 18 (32·8 per cent) of 55 patients with type IV-A cyst, mainly in the hilum, confluence or umbilical ducts (*Table 1*). These were divided into simple strictures and membranous strictures resembling septal duodenal stenosis in shape. Widening of the ductal lumen (ductoplasty), or some additional procedure, was performed for free bile drainage in all strictures (*Fig. 2*).

Simple stricture. This was observed at the hilum or confluence duct of 16 patients and was successfully repaired by ductoplasty at the hilum in all but one. The exception was a 17-year-old female patient who underwent cyst excision and end-to-end hilar anastomosis with Roux-en-Y jejunum[4]. A cholangiogram taken at initial surgery indicated a slight stricture of the left hepatic duct near the hilum, but the stricture was ignored. At the age of 32 years, 15 years after surgery, she suffered from epigastric pain, fever and jaundice. Percutaneous transhepatic cholangiography (PTC) confirmed intrahepatic gallstones with a moderate stricture of the left hilar duct which was accelerated by the incomplete hilar ductoplasty. Reoperation revealed no anastomotic stricture but atrophy of the lateral left hepatic segment. Lateral segmentectomy only was performed with a favourable outcome.

Table 1 Co-existing biliary anomalies and anatomical variations in 104 choledochal cysts

Primary ductal stricture	18
Hilar	14*
Confluence	2
Umbilical	2
Aberrant posterior duct	2
Low confluence of hepatic duct	2
Aberrant hepatic artery	2
Very small hepatic duct	2
Total	26

*Three right, 11 left

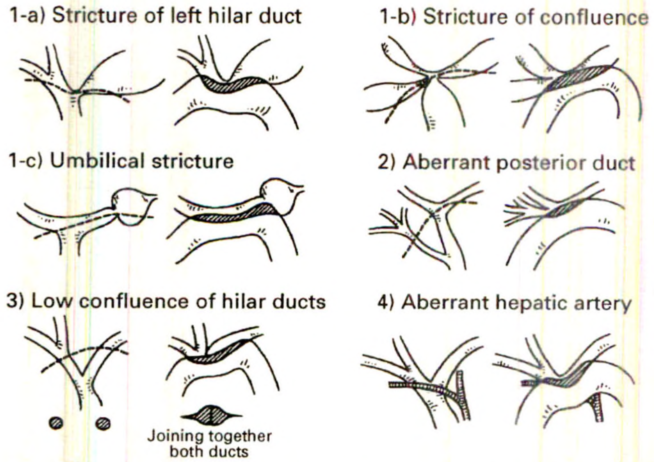
1-a) Stricture of left hilar duct
1-b) Stricture of confluence
1-c) Umbilical stricture
2) Aberrant posterior duct
3) Low confluence of hilar ducts
4) Aberrant hepatic artery
Joining together both ducts

Fig. 2 Co-existing biliary anomalies and anatomical variants in choledochal cyst (left) and corrective procedures (right). Dotted lines indicate incision line

Membranous stricture. This was seen at the umbilicus in two patients. In a 9-year-old girl an operative cholangiogram revealed choledochal cyst with umbilical ductal stricture (*Fig. 3*). Dissection from the hilum to the umbilicus disclosed a membranous stricture, similar to a septal duodenal stricture in shape, and a long bilioduodenostomy was successfully performed after excision of the membrane. Computed tomography (CT) taken 3 months after operation showed that cystic dilatation at the umbilicus was reduced in size. The girl is now 15 years old and in good health.

Aberrant posterior hepatic duct

An aberrant posterior hepatic duct draining into the distal common hepatic duct was observed in a child aged 2 years[8] (*Fig. 2*). The aberrant duct was excised and joined to the hepatic duct at the hilum, after which hilar hepaticoduodenostomy was performed with a large stoma created by incisions extending along the lateral wall of both the hepatic and aberrant ducts.

Low confluence of the right and left hepatic ducts

Low confluence was observed in two patients where hepatic ducts joined at the low hilar level (*Fig. 2*). Hilar anastomosis was performed after cutting off both the

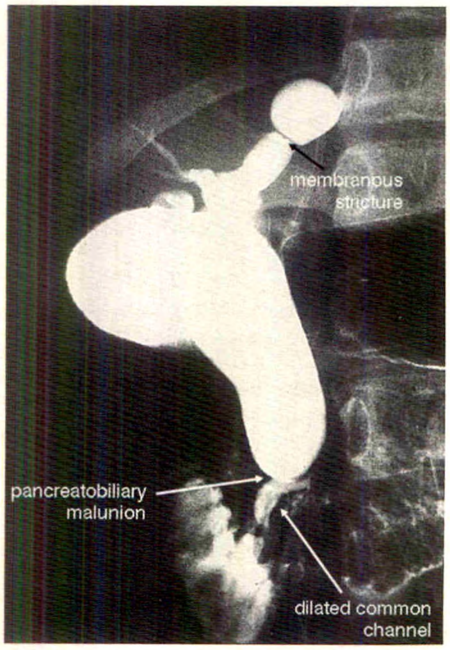

Fig. 3 Cholangiogram in a girl aged 9 years showing a membranous stricture at the umbilical portion. A long cholangioduodenostomy was performed after removal of the membrane

hepatic ducts, joining them at the hilum and making incisions in the lateral walls to create a large stoma.

Aberrant hepatic artery

The aberrant hepatic artery running in front of the common hepatic duct was observed in two children. It was easily replaced behind the jejunal loop as in normal anatomy at the time of biliary reconstruction (*Fig. 2*).

Very small bile duct

In two infants with type I cysts, the hilar and intrahepatic ducts were too small to perform a mucosal anastomosis between the duct and intestine[9]. After excision of the common hepatic duct at the hilum, the lateral walls of the hilar duct were incised to create a large stoma. The ductal mucosa was then everted and fixed to the liver parenchyma to prevent stricture formation. Finally, Kasai's procedure (hepatic portojejunostomy) was performed. Both children are now doing well 3 and 4 years after surgery respectively.

Discussion

Type IV-A cysts with intrahepatic involvement are often accompanied by a relatively narrow common hepatic duct smaller than the size of the intrahepatic ductal dilatation. Consequently, anastomosis between the common hepatic duct and bowel (conventional hepaticoenterostomy below the hilum) often produces a relatively narrow anastomosis which may lead to inadequate bile drainage from the liver and may aggravate anastomotic stricture with intrahepatic gallstones. Anastomotic strictures interfere with free bile drainage and cause bile stasis resulting in recurrent cholangitis. Reoperation for such instances is usually necessary 5 or more years after the initial surgery[4]. Removal of intrahepatic gallstones with a percutaneous transhepatic cholangioscope necessitates lengthy hospital stay and often results in unsatisfactory outcomes[4]. Early reoperation is necessary to improve the quality of life with short hospitalization when an anastomotic stricture with intrahepatic stones has been verified. Intrahepatic dilatation often regresses following adequate biliary decompression. Accordingly, a large hepaticoenterostomy across the bifurcation after complete removal of the extrahepatic bile duct should be performed primarily to prevent ascending cholangitis.

Type IV-A cyst also occasionally involves a primary ductal stricture which is detected by appropriate cholangiography, direct observation or intraoperative endoscopy[10]. Primary ductal stricture probably leads to intrahepatic ductal dilatation and gallstones[5,6,11,12], and may be classified into simple and membranous strictures[13]. Simple strictures are usually found in the intrahepatic duct near the hilum and are easily corrected by hilar ductoplasty and large hepaticoenterostomy[4,7]. However, it is occasionally overlooked because of an unsatisfactory cholangiogram and may become more severe as inflammatory attacks develop more frequently.

Membranous stricture tends to be found at the umbilicus. This can be excised by ductal dissection from the hilum to the umbilicus, following which a long cholangioenterostomy incorporating a hilar anastomosis obtains free bile drainage from the liver[5,13,14] (*Fig. 2*). When the left hepatic lobe is diseased, lateral segmentectomy is feasible[15]. Moreover, stricture of the upper duct rather than the umbilicus may require selective hepatectomy to eliminate the complicated lobe or repeated bouginage.

Complete removal of the extrahepatic and intrapancreatic bile ducts, and a wide hilar hepaticoenterostomy after ductoplasty around the hilum, or occasionally to the umbilicus, are essential procedures at primary surgery for choledochal cyst. Careful life-long follow-up should also be a routine part of the treatment, regardless of intrahepatic involvement. Given a wide anastomosis, favourable results can be expected in both the duodenostomy and jejunostomy groups[2,4] (*Fig. 1*).

Normal anatomical variants of the biliary tree or other anomalies in choledochal cyst are detected occasionally by cholangiography or direct vision at the time of surgery and frequently necessitate some procedure for their correction. An aberrant posterior hepatic duct draining into the distal common hepatic duct, however, seems to be rare[8]. The aberrant duct is excised and joined with the hilar hepatic duct, and hilar hepaticoenterostomy is performed with a large stoma. If the aberrant duct were ligated the posterior segment of the right lobe may develop biliary infection and result in subsequent atrophy.

In the low confluence of the right and left hepatic ducts, the anastomotic site around the confluence receives less blood supply than that in the hepatic hilum and may result in stricture. Accordingly, both hepatic ducts are excised at the hilum, anastomosed, and then both lateral walls are incised to provide a wide anastomotic stoma.

The aberrant hepatic artery running in front of the common hepatic duct is easily displaced behind the jejunal loop as in normal anatomy.

In some infants with choledochal cyst, hilar and intrahepatic ducts are too small to perform mucosal anastomosis between the duct and the intestine[9]. Anastomosis using a cuff of cyst to obtain sufficient stomal size is possibly unsuitable because it leaves the epithelium prone to stricture or cancer. After excision of the common hepatic duct at the hilum, incisions are performed in both hepatic ductal walls, after which the ductal mucosa is everted and fixed to the liver parenchyma to prevent stricture formation. Finally, Kasai's hepatic portojejunostomy remains the treatment of choice.

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Randomized trial of early *versus* delayed laparoscopic cholecystectomy for acute cholecystitis

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Background The aim of this prospective randomized study was to define the optimum management between early and delayed laparoscopic cholecystectomy for patients with acute cholecystitis.

Methods Patients were randomized to receive either early laparoscopic cholecystectomy within 24 h of randomization or initial conservative treatment followed by delayed laparoscopic cholecystectomy 6–8 weeks later.

Results There were 53 patients in the early group and 51 in the delayed group. There was no significant difference in conversion rate (early 21 per cent *versus* delayed 24 per cent), postoperative analgesic requirement (1 *versus* 2 doses) and postoperative complications. However, the early group had significantly longer operating time (122·8 *versus* 106·6 min, $P = 0{\cdot}04$) and shorter total hospital stay (7·6 *versus* 11·6 days, $P < 0{\cdot}001$).

Conclusion Early laparoscopic cholecystectomy is safe and feasible for acute cholecystitis with the additional benefit of shorter total hospital stay. Apart from a shorter operating time, treating patients with delayed laparoscopic cholecystectomy does not offer additional benefit.

Laparoscopic cholecystectomy has become the 'gold standard' for the treatment of symptomatic gallstones and chronic cholecystitis. However, there are still controversies over the use of laparoscopic cholecystectomy to treat acute cholecystitis. In the developmental stage of laparoscopic cholecystectomy it was considered 'unsafe' or 'technically difficult' to perform laparoscopic cholecystectomy for acute cholecystitis[1,2]. With increasing experience in laparoscopic surgery, a number of centres have reported on the use of laparoscopic cholecystectomy for acute cholecystitis, suggesting that it is technically feasible but at the expense of a high conversion rate, which can be up to 35 per cent[3–5].

Several randomized studies in the early 1980s had shown that performing early open cholecystectomy for acute cholecystitis was better than delayed cholecystectomy in terms of shorter hospital stay but both had similar operative morbidity and mortality rates[6,7]. Early surgery had since gained in popularity in the late 1980s[8].

In this laparoscopic era, the optimal time to carry out laparoscopic cholecystectomy for acute cholecystitis remains controversial and there are no prospective data to settle this issue. Successful laparoscopic cholecystectomy during the period of acute inflammation is associated with an earlier recovery and shorter hospital stay when compared with open cholecystectomy[9]. The potential advantages of early laparoscopic cholecystectomy can, however, be offset by a high conversion rate to open surgery. On the other hand, initial conservative treatment may lead to a technically easier delayed laparoscopic cholecystectomy after the acute inflammation has subsided, thus leading to a lower conversion rate. A prospective randomized study was performed to compare early and delayed laparoscopic cholecystectomy in the treatment of acute cholecystitis.

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Patients and methods

Patient selection and study design

Approval for the study was obtained from the hospital ethics committee. From January 1993 to December 1995 all patients with a diagnosis of acute cholecystitis admitted to the surgical department at the Prince of Wales Hospital, Hong Kong, were considered eligible for the study. The diagnosis of acute cholecystitis was based on a combination of a compatible clinical picture (acute right upper quadrant tenderness, temperature greater than 37·5°C and white blood cell count greater than 10×10^9/l) and ultrasonographic evidence of acute cholecystitis (presence of gallstones in a thickened and oedematous gallbladder, positive sonographic Murphy sign and pericholecystic fluid collections)[10]. Patients were excluded from randomization if they: (1) had symptoms present for more than 1 week; (2) had had previous upper abdominal surgery; (3) had significant medical diseases that rendered them unfit for laparoscopic surgery; or (4) had coexisting common bile duct stones with ductal dilatation, acute cholangitis or acute pancreatitis. Informed consent was obtained. Patients were then randomized into either the 'early' group or the 'delayed' group according to a computer-generated randomization list kept by a third party.

In the early group laparoscopic cholecystectomy was performed within 24 h of randomization whereas in the delayed group conservative treatment with intravenous fluid and antibiotics including ampicillin, cefuroxime and metronidazole was given. Patients who responded to conservative treatment had elective laparoscopic cholecystectomy 6–8 weeks after the acute episode had subsided. On the second admission patients were routinely admitted 1 day before the scheduled operation. Patients who failed conservative treatment with worsening clinical signs or those who developed a recurrent attack of acute cholecystitis before the scheduled delayed cholecystectomy were treated with emergency laparoscopic cholecystectomy.

Quality assurance and the surgical procedure

Laparoscopic cholecystectomy, whether early or delayed, was performed by a group of eight experienced laparoscopic surgeons who each had performed more than 50 cases. The surgical procedure was similar to that described previously[4]. Pneumoperitoneum was created by the open technique. Dissection with electrocautery was used. The cystic duct was secured with polydioxanone clips and the cystic artery with titanium clips. Operative cholangiography was not performed routinely. Closed suction drains were inserted through the subcostal port to drain the subhepatic space at the end of the procedure. Resected gallbladders were sent for pathological examination. Intramuscular pethidine at a dose of 1 mg/kg every 4 h was offered on demand after operation.

Study parameters

Data were collected prospectively and included patient demographics, operative findings, conversion to open cholecystectomy and the reason for conversion, operating time, postoperative analgesic requirement, length of postoperative stay and total hospital stay (including the admission on presentation and admission for subsequent delayed surgery in the delayed group), and postoperative complications.

Sample size calculations and statistical analysis

In the authors' department the historical conversion rate for early laparoscopic cholecystectomy for acute cholecystitis was about 25 per cent. Based on the objective of detecting a 20 per cent reduction in the conversion rate in the delayed cholecystectomy group, sample size calculation revealed that for $\alpha = 0{\cdot}05$ (one-tailed) and statistical power = 0·8, at least 48 patients were needed in each group. Statistical analysis was performed with the *t* test, Mann–Whitney *U* test and χ^2 test as appropriate. $P < 0{\cdot}05$ was considered statistically significant.

Results

During the study period 31 patients were excluded before randomization and 104 were randomized (*Fig. 1*). Of the 53 patients randomized to the early group, 23 were men; mean(s.d.) age was 55·8(14·6) (range 25–78) years. In the delayed group there were 15 men; mean(s.d.) age was 56·1(14·4) (range 31–81) years. There was no significant difference between the sex ratio ($P = 0{\cdot}20$, χ^2 test) and the age of the patients in both groups ($P = 0{\cdot}90$, *t* test).

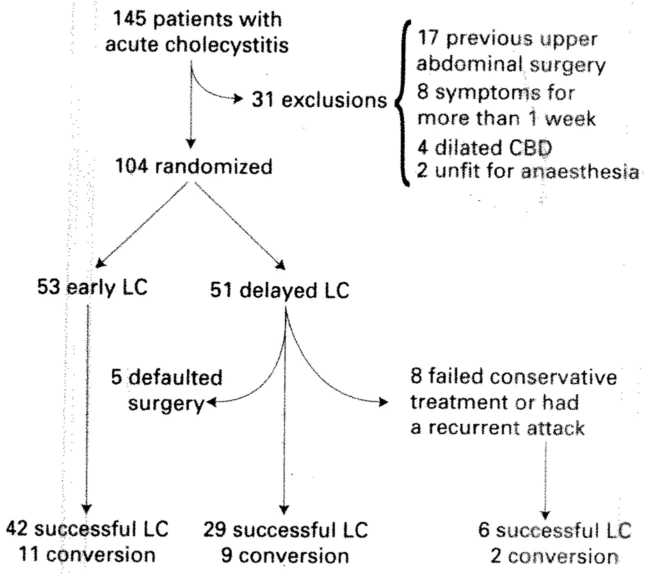

Fig. 1 Management scheme for the 145 patients with acute cholecystitis in the study. CBD, common bile duct; LC, laparoscopic cholecystectomy

Outcome

In the delayed group five patients defaulted surgery after successful conservative treatment. Emergency laparoscopic cholecystectomy was performed because of failed conservative treatment in seven patients and a recurrent attack of acute cholecystitis before the scheduled delayed cholecystectomy in one patient. Among these eight patients who had emergency laparoscopic cholecystectomy, there were two conversions to open surgery. No complication was noted in this group of patients.

Conversions to open surgery and operating time

Eleven (21 per cent) of the 53 patients in the early group and nine (24 per cent) of the 38 in the delayed group required conversion to open surgery ($P = 0{\cdot}74$, χ^2 test). The main reason for conversion in the delayed group was adhesions around Calot's triangle and the gallbladder, making dissection and identification of anatomical structures difficult. In the early group, additional inflammation or gangrenous changes of the gallbladder prevented successful dissection in some cases. Mean(s.d.) operating time in the early group was 122·8(36·0) (range 60–230) min and that in the delayed group was 106·6(37·3) (range 45–195) min ($P = 0{\cdot}04$, *t* test). If patients who had conversion were excluded, mean operating time in the early group was 118·8 min compared with 96·9 min in the delayed group ($P = 0{\cdot}02$, *t* test).

Postoperative complications

There was no major bile duct injury or death. The overall complication rate in the early group was 9 per cent (five of 53 patients) and in the delayed group 8 per cent (three of 38 patients) ($P = 0{\cdot}80$, χ^2 test). In the early group three patients developed subphrenic collections, two of which required ultrasonographically guided percutaneous aspiration. The other patient responded to conservative treatment with antibiotics. One patient had undetected common bile duct stones at operation and developed bile leakage from the cystic duct stump. He was treated with percutaneous drainage of the collection and common bile duct stone extraction by endoscopic retrograde cholangiopancreatography. One other patient developed a minor wound infection. In the delayed group one patient developed a subphrenic collection which required percutaneous aspiration, one had a minor wound infection and another postoperative respiratory failure which required mechanical ventilation for 3 days.

Postoperative analgesic requirement

Median postoperative analgesic requirement in the early group was 2 (range 0–17) doses of pethidine and in the delayed group 1 (range 0–7) dose ($P = 0{\cdot}14$, Mann–Whitney *U* test).

Pathological examination of resected gallbladders

In the early group all 53 resected gallbladders showed histological features of acute cholecystitis, and three had signs of gangrenous cholecystitis. In the delayed group all gallbladders showed features of chronic cholecystitis.

Total length of hospital stay

Mean(s.d.) total hospital stay in the early group was 7·6(3·6) (range 4–21) days and in the delayed group 11·6(3·4) (range 5–24) days ($P < 0·001$, *t* test). However, mean(s.d.) postoperative hospital stay in the early group was 4·8(3·1) (range 2–17) days and in the delayed group 3·0(1·9) (range 1–10) days ($P < 0·001$, *t* test). Mean(s.d.) preoperative hospital stay in the early group was 1·7(1·0) (range 0–3) days and in the delayed group 1·3(0·5) (range 1–2) days.

Discussion

In the early years of laparoscopic surgery acute cholecystitis was regarded as a relative contraindication to laparoscopic cholecystectomy[1,2]. It is only recently that laparoscopic cholecystectomy has been shown to be a feasible and safe procedure for acute cholecystitis[11,12]. The rate of conversion to open surgery in acute cholecystitis was reported to range from 6 to 35 per cent[3,11,13,14], which was higher than that for symptomatic gallstones. This reflects the increased technical difficulties in laparoscopic surgery for the acutely inflamed gallbladder. However, a high conversion rate to open surgery obviates the advantages of laparoscopic cholecystectomy. It can, therefore, be argued that, if 'delayed' laparoscopic cholecystectomy leads to a technically easier laparoscopic surgery with a resultant lower conversion rate[15], it may be a better treatment option for acute cholecystitis.

Such an assumption that initial conservative treatment will increase the chance of successful laparoscopic cholecystectomy at a later date and possible better outcome cannot be substantiated by this study. The delayed group had a slightly higher rate of conversion to open surgery, although the difference was not significant (21 per cent in the early group *versus* 24 per cent in the delayed group). In fact, the increase in dense adhesions around the gallbladder and porta hepatis after initial conservative treatment makes the laparoscopic dissection more difficult in a proportion of patients[12,14,15] and constitutes the main reason for conversion to open surgery. Eight patients (16 per cent) randomized to the delayed group failed conservative treatment or developed a recurrent attack of acute cholecystitis requiring emergency laparoscopic cholecystectomy, a value in good agreement with other studies[7,16].

The more frequent requirement to adopt technical modifications such as needle aspiration of the gallbladder, insertion of extra retraction ports or the use of plastic bags for gallbladder extraction to avoid contamination may well explain the longer operating time required in the early group. Postoperative complications and postoperative analgesic requirements were similar in both groups. The absence of major complications such as bile duct injury suggests that laparoscopic cholecystectomy can be performed safely in both early or delayed settings. Although the postoperative stay was longer in the early group, the total hospital stay (counting both admissions) was longer in the delayed group.

It is a general impression that there exists a range of different gallbladders from minimally inflamed to grossly thickened oedematous or even gangrenous cholecystitis with increasing technical difficulties. The diagnostic criteria for acute cholecystitis used in this study combined clinical and radiological diagnoses. As evidenced by histopathological examination of the gallbladders, the accuracy of the diagnosis of acute cholecystitis was 100 per cent in the early group. This confirmed that the patients did have acute cholecystitis and not simply biliary colic. However, under the exclusion criteria of the present study, some patients with severe acute or gangrenous cholecystitis who presented with symptoms of more than 1 week in duration might have been excluded. Although it has been shown that these patients have a very high conversion rate if early laparoscopic cholecystectomy is attempted[3], they constituted only 6 per cent of patients (eight of 145) in this study. Therefore, the effects of excluding these patients from the study would not be substantial.

In conclusion, both early and delayed laparoscopic cholecystectomy are feasible and safe in the treatment of acute cholecystitis. However, delayed laparoscopic cholecystectomy is not associated with a lower conversion rate. Like open cholecystectomy, early laparoscopic cholecystectomy offers definitive treatment during the same admission and avoids the problems of failed conservative treatment and delayed surgery. Furthermore, a reduction of total hospital stay is a major economic benefit to the current healthcare system.

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Role of arteriography in the selection of patients for carotid endarterectomy

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Background Duplex ultrasonography is used increasingly to select patients for carotid endarterectomy. This study aims to clarify whether arteriography is still required.

Methods A total of 272 patients in whom duplex imaging indicated significant disease of the internal carotid artery underwent arteriography and the results were compared. Regarding the arteriogram as the 'gold standard', three aspects were considered: the accuracy of duplex ultrasonography in detecting significant stenosis, the ability of duplex imaging to identify patients who should have arteriography and whether the arteriogram provided important additional information that might influence a decision to operate.

Results Three patients (1 per cent) suffered a permanent neurological deficit as a result of arteriography. Of the 272 patients with significant stenosis identified by duplex ultrasonography, 241 (89 per cent) were confirmed as significant on arteriography. Duplex imaging was not able to predict accurately which arteriograms would provide useful additional information (sensitivity 59 per cent, specificity 65 per cent), whereas 89 arteriograms (33 per cent) contained information that might have influenced subsequent management.

Conclusion Duplex imaging is unable to detail the anatomy or determine the extent of carotid disease and may therefore lead to an inappropriate decision to perform carotid endarterectomy. Duplex imaging alone is not adequate before carotid endarterectomy.

Over the past decade there has been a gradual evolution in the preoperative assessment of patients for carotid endarterectomy towards less invasive investigation. This trend has resulted from the recognition of the significant risks associated with arteriography[1-9] and the increasing accuracy of modern duplex imaging. In the past, patients with symptoms attributable to carotid artery disease were initially investigated with duplex imaging and in those with evidence of significant stenosis of the internal carotid artery arteriography was performed to confirm the extent of disease. Since publication of the two multicentre trials, the North American Symptomatic Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), which proved the efficacy of carotid endarterectomy, several studies[10-14] have attempted to develop duplex imaging criteria that correlate with the grading of arteriographic stenosis. Consequently many surgeons now regard carotid arteriography as unnecessary before surgery.

While the degree of carotid stenosis is clearly vital in determining treatment, other factors such as the extent of proximal or distal disease are equally relevant; in this respect, arteriography has advantages. The relative positions of anatomical structures (e.g. internal carotid artery and mandible) that arteriography readily demonstrates are also important in decision making. This study compares carotid arteriography with duplex imaging and considers whether duplex imaging alone provides sufficient information to determine whether carotid endarterectomy should be performed.

Patients and methods

Between January 1992 and May 1995, 285 consecutive patients (153 men and 132 women of mean age 67 years) with duplex scans indicating significant disease of the internal carotid artery underwent arteriography. These patients gave a history consistent with disease affecting the relevant carotid artery territory (e.g. previous stroke, amaurosis fugax, transient ischaemic attack). The study commenced with the introduction of a new colour duplex scanner (Acuson 128; Acuson, Uxbridge, UK) and concluded just before the introduction of digital subtraction arteriography as the standard technique for performing carotid arteriography. Throughout the 40-month study the imaging apparatus remained the same.

Duplex imaging was performed by one of two experienced vascular technicians before arteriography. Criteria for stenosis were based on velocity and waveform analysis, and haemodynamically significant stenoses were taken to be those with a doubling of the velocity at the carotid bifurcation with associated broadening of waveform on spectral analysis. The proximal common carotid and the proximal segment of the external carotid artery were both scanned routinely.

All patients in the study had both carotid arteriography and duplex imaging performed. The ability of sonographers to predict which patients required arteriography to clarify an abnormality identified on the scan was assessed prospectively. This applied to the last 86 patients in the study and the decision was based on the following criteria: (1) an atheromatous plaque was identified but its extent could not fully be ascertained, either because it was too high to image completely or because the plaque extended for more than 2 cm; (2) the stenosis was a significant distance from the carotid birfurcation; and (3) calcification of the plaque or vessel wall interfered with the ultrasound signal.

Carotid arteriography was carried out via the transfemoral or transbrachial approach with selective catheterization of the common carotid artery. It is policy of the unit to perform only lateral uniplanar views of the carotid vessels which also display the cerebral circulation. It is recognized that a uniplanar view

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will give less information than multiplanar views but the requirement for two contrast injections in the latter case was thought to have the potential to increase complication rates.

Assessment of the arteriograms was made prospectively (without knowledge of the duplex result) by a vascular surgeon in conjunction with a sonographer from the vascular laboratory. The degree of stenosis of the internal carotid artery (based on the mean value of the two observers) was calculated by comparing the luminal diameter at the stenosis with that of the internal carotid artery distal to the lesion, consistent with the NASCET[13] method. Whilst the ECST[14] study reached similar conclusions to the NASCET at the stenosis greater than 70 per cent threshold, the method of stenosis measurement was different and it has been estimated that a 50 per cent stenosis from the NASCET study was equivalent to 70 per cent from the ECST[15]. Thus, for the purposes of this study any stenosis greater than 50 per cent on arteriography was regarded as significant.

If there was difficulty in measuring the stenosis accurately on the arteriogram (because of poor definition), the presence of this potential error was documented. Any additional information provided by the arteriogram which might alter the patient's management was recorded. The mean time lapse between duplex imaging and arteriography was 45 (median 41) days.

The number of patients having carotid endarterectomy and the complication rate were recorded to determine whether arteriography had influenced the decision to operate.

Results

No patient died as a consequence of arteriography, although two developed a persisting hemiparesis and a further patient had a visual field deficit following the procedure (1 per cent rate of persisting neurological deficit). Additionally two patients developed a groin haematoma.

Carotid arteriography and duplex imaging were performed on 285 patients; in 13 the arteriogram either failed or was not of sufficient quality to allow worthwhile comparison with the duplex scan. The accuracy of duplex imaging was therefore obtained by comparison with arteriography in 272 patients.

Duplex imaging correctly identified a significant stenosis in 241 patients (89 per cent). A similar analysis was performed after excluding all patients whose arteriograms were subject to observer error (i.e. accuracy in stenosis measurement could not be achieved). In this case, using 183 comparisons, duplex ultrasonography correctly identified a significant stenosis in 166 patients (91 per cent). Overall, useful information was obtained from the arteriograms in 89 (33 per cent) of the 272 comparisons performed (*Table 1*).

In 86 consecutive patients the sonographer was asked to indicate whether an arteriogram was advised based on information obtained from the scan. This opinion was then compared with the arteriogram result with respect to whether arteriography provided useful additional information. Duplex imaging had a sensitivity of 59 per cent and a specificity of 65 per cent with respect to evaluation of this selective arteriography policy.

Table 1 Additional information provided by arteriography in 89 patients

	No. of patients
Stenosis less than 50 per cent	25
High carotid birfurcation	23
Extensive distal atheroma	18
Very narrow internal carotid	10
Internal carotid occlusion	4
Tortuous internal carotid	5
Siphon disease	3
Proximal atheroma	1

Of the 272 comparisons, carotid endarterectomy was performed in 215 cases with an operative mortality rate of 1 per cent and an overall stroke rate of 8 per cent. In 26 patients surgery was not performed because of information obtained from the arteriogram.

Discussion

The need for preoperative arteriography before carotid endarterectomy was first challenged in 1982 when Blackshear and Connar[16] operated on four patients without arteriographic assessment. Since then a policy of selective arteriography has become widespread. It is now known that symptomatic patients with a 30–70 per cent carotid stenosis are equally well treated by medical therapy[17] or carotid endarterectomy, whereas those with stenosis of less than 30 per cent have a better outcome on medical therapy[14]. Finding a less invasive imaging technique than arteriography to distinguish between the group that will benefit from surgical rather than medical treatment is attractive, especially if it reduces overall morbidity. The risk of arteriography is significant (1 per cent had a persisting neurological deficit in this study, similar to other reports) and appears to be higher in patients with severe aortoiliac disease, renal insufficiency or documented allergy to the contrast medium. The risks in all patients with cerebrovascular disease are also increased[1]. The significant failure rate (5 per cent in this study), delays incurred waiting for the procedure and cost are notable disadvantages of arteriography.

By contrast, carotid duplex imaging is non-invasive, rapid and can be repeated on the same day as surgery. While arteriography has previously been regarded as the 'gold standard', and large multicentre trials proving the efficacy of endarterectomy have been based on it, duplex imaging may become the most appropriate test because it relies on dynamic flow disturbance rather than static images. Indeed, studies that have correlated arteriographic stenosis measurement with equivalent criteria for duplex imaging show great variation. Duplex imaging is operator dependent and each individual laboratory should audit its results carefully to ensure continuing quality.

Duplex imaging does have limitations: neither the aortic arch and proximal cranial branches nor the intracranial circulation, and in particular siphon disease, can be assessed. Proximal disease or contralateral occlusion can interfere with accurate classification of stenosis by affecting flow rates. The fact that these limitations are important in determining treatment is highlighted by this study in which 89 of the 272 arteriograms reviewed contained useful additional information and in 26 cases resulted in a change of management and a decision not to operate. Ideally, this group, which requires arteriography, could be identified by duplex scanning. Some have suggested a policy of selective arteriography but in this study, the sonographers were not able to select a group in which arteriography might demonstrate useful additional information, i.e. only 59% of those predicted by duplex imaging had extra information on arteriography.

Determining the severity of carotid stenosis is clearly crucial in decision making and, whilst duplex can achieve this[10–12], there is no evidence that patients who have endarterectomy after a duplex scan alone achieve a good long-term result compared with a control group. In this study, relying on duplex imaging alone would have resulted in an additional 31 patients having carotid endarterectomy.

No other imaging technique has allowed as accurate an assessment as duplex ultrasonography or arteriography, but magnetic resonance imaging may provide risk-free arteriography in the future, either alone or in combination with duplex imaging[18].

The results of this study demonstrate that duplex imaging is accurate in detecting haemodynamically significant stenosis but, in a proportion of cases, it fails to identify essential anatomical details and the extent of proximal or distal disease. Therefore, whilst it is suitable for screening, duplex imaging alone cannot determine whether surgery should be performed. By comparison, arteriography provides complete information and therefore should be performed in all patients before carotid endarterectomy.

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Cerebral haemodynamics and embolization during carotid angioplasty in high-risk patients

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Background Patients with symptomatic internal carotid artery (ICA) stenosis greater than 70 per cent in association with a contralateral ICA occlusion may have an increased risk of stroke following carotid endarterectomy. Such patients might benefit from the theoretically shorter ischaemic time offered by carotid angioplasty and stenting.

Methods Nine patients who underwent carotid angioplasty and stenting were monitored using near-infrared spectroscopy, continuous jugular venous oximetry and transcranial Doppler ultrasonography to detect both haemodynamic ischaemia and embolic events.

Results Significant ischaemia occurred in four of the nine patients once the stenosis had been crossed by the guidewire (spectroscopy and oximetry). Inflation of the angioplasty balloon resulted in a brief period of ischaemia and showers of emboli in all patients (ultrasonography) and this persisted for more than 3 min after balloon deflation in three patients. One patient had a major disabling stroke due to ICA thrombosis.

Conclusion Angioplasty and stenting in these high-risk patients may not confer any advantage over conventional surgery in terms of both haemodynamic ischaemia and embolization.

Percutaneous transluminal angioplasty (PTA) and stenting are established in the treatment of peripheral[1], coronary[2] and renal[3] arteriosclerosis. Although the benefit of carotid endarterectomy for severe symptomatic carotid disease is now proven[4,5], PTA–stenting is being advocated as an alternative[6]. In particular it is suggested that carotid angioplasty offers both clinical and economic advantages, being less invasive, avoiding general anaesthesia and allowing shorter hospital admission[6]. While the results of small published series appear encouraging[7–9], there have been no controlled trials comparing the outcome with surgery.

A potential advantage of PTA is the shorter ischaemic time associated with angioplasty balloon inflation compared with surgery. Conversely PTA is associated with release of multiple emboli[10], the effect of which cannot be predicted.

Patients at risk from haemodynamic ischaemia during surgery are those with a severe internal carotid artery (ICA) stenosis and a contralateral ICA occlusion[11–13]. These patients might benefit from PTA–stenting. The present study used transcranial Doppler ultrasonography (TCD), near-infrared spectroscopy (NIRS) and continuous jugular venous oximetry to monitor a group of high-risk patients undergoing carotid PTA–stenting.

Patients and methods

After obtaining ethics committee approval, patients with an ultrasonographically detected symptomatic ICA stenosis greater than 70 per cent and occlusion of the contralateral ICA underwent selective transfemoral carotid angiography to confirm the severity of the carotid disease. In an 18-month interval nine patients gave informed consent to undergo PTA–stenting. Their demographic details, symptoms and disease severity are shown in *Tables 1* and *2*.

Angioplasty–stenting

All interventions were performed by a single neuroradiologist under a standard isoflourane-based general anaesthetic. General anaesthesia was used on the basis that the procedure might be prolonged during the early experience and to facilitate accurate stent placement during controlled apnoea. The angiography

Table 1 Clinical details

Sex ratio (M:F)	5:4
Median (range) age (years)	67 (45–79)
Co-morbidity	
Treated hypertension	5
Ischaemic heart disease	4
Intermittent claudication	2
Diabetes mellitus	0
Smoker	4

Table 2 Carotid disease: symptoms and severity

Presentation	
Amaurosis fugax	3
Transient ischaemic attack	5*
Stroke	1
Median (range) ipsilateral stenosis (%)	80 (75–90)
Contralateral internal carotid artery occlusion	9

*Including two with contralateral haemodynamic transient ischaemic attacks

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Table 3 Middle cerebral artery velocity, jugular venous oxygen saturation and changes in the concentration of cytochrome oxidase measured from an arbitrary baseline of zero during carotid percutaneous transluminal angioplasty–stenting

	Baseline	Guidewire	Inflation	Hyperaemia	At end of surgery
MCAV (cm/s)	72 (34–84)	48 (25–72)	0 (0–48)	88 (52–133)	81 (34–133)
$[caa_3]$ (μ mol/l)	0	− 0·2 (− 2·7–0)	− 0·4 (− 2·0–0·1)	0 (− 1·0–0·2)	0·2 (− 2·8–0·5)
$SJvO_2$ (%)	70 (56–80)	68 (49–75)	64 (43–70)	69 (55–80)	75 (60–85)

MCAV, middle cerebral artery velocity; $[caa_3]$, concentration of cytochrome oxidase; $SJvO_2$, jugular venous oxygen saturation

catheter was positioned in the common carotid artery via one femoral artery while the guidewire and angioplasty balloon–stent were delivered via the other groin. Intra-arterial heparin (5000 units) was given after positioning the guidewire. The first patient underwent angioplasty alone, whereas an ICA stent was deployed in the remaining patients (Palmaz stent, Johnson and Johnson Interventional Systems, Warren, New Jersey, USA, $n = 2$; Strecker stent mounted on an Ultrathin angioplasty catheter, Meditech, Boston Scientific, Watertown, Massachusetts, USA, $n = 6$). All stents measured 20–40 × 5–6 mm and were deployed with a 15-s inflation. Further inflations were used to expand the stent fully if required. Intravenous heparin was given for 72 h after the procedure. Thromboprophylaxis was continued with self-administered enoxaparin, 20 mg daily for 6 weeks, and long-term enteric-coated aspirin (300 mg daily).

Monitoring

Transcranial Doppler ultrasonography. Ipsilateral middle cerebral artery velocity (MCAV) was measured with a transcranial Doppler ultrasonographic probe (EME Pioneer TC2020; Nicolet Instruments, Warwick, UK) positioned over the temporal window and held with a headstrap. This instrument includes emboli detection software (data saved for off-line analysis), and Spencer's criteria[14] were used to distinguish artefact from embolus. No attempt was made to differentiate between air and particulate emboli. MCAV measurements were also stored on computer disk.

Near-infrared spectroscopy. The Critikon Cerebral Redox Research Monitor 2001 (Johnson and Johnson, Ascot, UK) measures trends in the cerebral concentrations of oxyhaemoglobin $[HbO_2]$, deoxyhaemoglobin [HHb] and cytochrome oxidase $[caa_3]$. A decrease in $[HbO_2]$ with an increase in [HHb] indicates increased cerebral oxygen extraction (tissue ischaemia), while a decrease in $[caa_3]$ is believed to represent cellular ischaemia. The probe was attached to the forehead ipsilateral to the vessel for PTA–stenting.

Continuous jugular venous oximetry. Jugular bulb venous oxygen saturation ($SJvO_2$) was measured continuously with the Oximetrix III system (Abbott Instruments, Epsom, UK). After induction of general anaesthesia, one internal jugular vein was cannulated and the fibreoptic catheter was positioned with its tip in the jugular bulb. In six patients the dominant internal jugular vein, as judged by the angiogram, was used. In the remaining three patients, with equal venous drainage, the catheter was inserted on the side of the occluded ICA. During monitoring a fall in $SJvO_2$ reflected inadequate cerebral oxygen delivery.

Results

All interventions were technically successful with a reduction in median (range) stenosis from 80 (range 70–90) to 10 (0–30) per cent. However, one patient suffered a disabling stroke caused by acute thrombosis of the stented artery. One further patient, taking warfarin, developed a large retroperitoneal haematoma and another had a large groin haematoma. Neither required intervention. There were no other complications.

The patterns of change in MCAV, $SJvO_2$, $[HbO_2]$ and $[caa_3]$ were similar, with a fall on balloon inflation and reactive hyperaemia following angioplasty–stenting (*Table 3*). However, there were important variations: crossing the stenosis with the guidewire produced a significant reduction in MCAV, $SJvO_2$, $[HbO_2]$ and $[caa_3]$ in four of the nine patients and $[caa_3]$ remained depressed for more than 3 min after angioplasty–stenting in three of the patients, suggesting prolonged cellular ischaemia. Less importantly, balloon inflation resulted in a small, transient, increase in $SJvO_2$, $[HbO_2]$ and $[caa_3]$. This presumably reflected a brief augmentation in flow.

Emboli were detected in all patients during guidewire manipulation but most notably following balloon deflation. In addition, each bolus of contrast produced signals similar to showers of emboli. The median number of emboli was 128 (range 90–250) per patient and in one patient transcranial Doppler ultrasonographically detected emboli were associated with brief ischaemic episodes detected by both NIRS and jugular venous oximetry.

Two patients developed evidence of reperfusion hyperaemia following stent deployment with steadily rising MCAV, $SJvO_2$, $[HbO_2]$ and $[caa_3]$. This was controlled by lowering the blood pressure until MCAV reached preangioplasty levels, then allowing the pressure to rise slowly again. Acute ICA spasm was noted in two patients but resolved without complications.

In the patient who developed an acute ICA thrombosis, two stents were deployed, one across the carotid bifurcation and the other in the distal common carotid artery. The angioplasty balloon became ensnared on one of the stents and, while attempts were being made to detach it, a reduction in cerebral perfusion was detected by all monitoring modalities. An initial angiogram demonstrated ICA spasm but, following a further fall in MCAV, angiography confirmed acute thrombosis. Although lysis was achieved with locally delivered tissue plasminogen activator after 15 min, and MCAV, $SJvO_2$ and $[HbO_2]$ returned to normal, $[caa_3]$ remained depressed and the total ischaemic time exceeded 20 min. The patient developed a dense hemiplegia and computed tomography confirmed ipsilateral infarction in the distribution of both the middle cerebral artery and watershed areas.

Discussion

The advantages of carotid PTA–stenting over surgery are less clear than for renal, coronary and peripheral arterial PTA. Proponents argue that it avoids general anaesthesia and requires a shorter hospital stay[6]. However, the potential complications of carotid PTA–stenting include intraprocedural embolic events and an unknown incidence of recurrent stenosis. Furthermore, carotid endarterectomy can be performed under regional anaesthesia with hospital admission as short as 24 h[15]. Finally, while the two major multicentre trials of carotid endarterectomy reported combined stroke–death rates of 5·8 and 7·5 per cent, the outcome in specialist centres may be better[16,17].

In this study multiple emboli were detected during all procedures, particularly on balloon deflation, confirming the findings of Markus *et al.*[10]. These were at least ten times more frequent than observed during carotid endarterectomy. Emboli were also detected during guidewire manipulation, which emphasizes the importance of minimizing instrumentation across the stenosis. Furthermore this suggests that the double balloon technique of Theron *et al.*[18], in which an additional balloon is inflated distal to the angioplasty site to trap embolic material, will not prevent all embolic events. Henry and co-workers (personal communication) found no reduction in stroke rate using this approach.

The clinical significance of cerebral emboli remains unclear. In the present study one patient, who had no neurological complications, showed evidence of cerebral ischaemia on $SJvO_2$ and NIRS monitoring, apparently related to showers of emboli. In addition Gaunt *et al.*[16] have shown that multiple emboli during carotid surgery cause subtle neuropyschological deficits. In the present study $SJvO_2$[19] and NIRS measurements provided a detailed assessment of the influence of altered cerebral blood flow on tissue oxygenation. When blood flow is inadequate, cerebral oxygen extraction increases and $SJvO_2$ falls. These measurements are complemented by NIRS which, although regarded as experimental, provides a direct measure of tissue oxygenation ($[HbO_2]$) and cellular ischaemia ($[caa_3]$)[20]. That the changes in $[HbO_2]$ and $SJvO_2$ were similar supports the validity of NIRS. Interestingly the $SJvO_2$ changes occurred several seconds later, reflecting the time taken for blood to travel from the cerebral hemisphere to the jugular bulb.

The changes in cerebral blood flow and oxygenation during PTA–stenting were similar to those following clamp application and release during carotid endarterectomy[21]. MCAV, $SJvO_2$, $[HbO_2]$ and $[caa_3]$ fell during balloon inflation, followed by transient hyperaemia on deflation. The initial overshoot in MCAV is likely to represent increased flow through a dilated vascular bed. Autoregulation takes several minutes to readjust. The parallel changes in the parameters of tissue oxygenation support this hypothesis.

Although PTA–stenting was used in these high-risk patients to reduce the duration of ischaemia, this did not always happen. In four patients MCAV fell following guidewire insertion resulting in prolonged ischaemic times of 8–22 min, longer than required for shunt insertion during carotid endarterectomy. Furthermore, cellular ischaemia (lower $[caa_3]$) persisted for more than 3 min in three patients after balloon deflation despite apparently adequate oxygen delivery (measured by $[HbO_2]$, $SJvO_2$, MCAV), suggesting a temporary uncoupling of oxygen utilization at a cellular level. Thus, in patients with multiple, severely diseased vessels, PTA–stenting may not deliver a shorter ischaemic time. Although a shunt can be inserted when ischaemia is detected during operation, there is no comparable strategy for PTA.

The present results may represent a learning process, but suggest that patients who have a high risk of embolic or haemodynamic ischaemia during surgery are also at risk during PTA–stenting. While PTA of other vessels often avoids the need for major surgery, if complications occur, or if PTA fails, remedial surgery is usually possible. Carotid PTA–stenting differs in this respect because surgery is unlikely to salvage any of the neurological complications of endovascular therapy.

Reservations have been voiced about the current enthusiasm for carotid PTA–stenting, including the view that the technique should be performed only within controlled trials[22]. Routine carotid PTA–stenting will be justified only if such trials confirm that both the early (stroke, death) and late (recurrent stenosis) results are as good as those for carotid endarterectomy.

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Prospective randomized trial of woven *versus* collagen-impregnated knitted prosthetic Dacron grafts in aortoiliac surgery

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Background Despite the theoretical advantages of coating knitted grafts with a material designed to reduce blood loss, their performance has not been directly compared with woven grafts in a prospective randomized trial. The aim of this study was to compare the graft handling qualities and operative blood loss of the two types of arterial prosthesis, as well as complication rate and patient survival at 1 year.

Methods A total of 267 consecutive patients having surgery for occlusive or aneurysmal disease of the aortoiliac arteries were randomized to receive woven (141 patients) or knitted collagen-impregnated Dacron (126 patients) grafts. Graft patency was assessed on discharge and at 1 year by duplex imaging.

Results Mean(s.d.) intraoperative blood loss was statistically greater with woven grafts (1690(1424) ml) compared with knitted (1363(1172) ml) ($P = 0{\cdot}049$). An insignificant 1-year increase in mean(s.d.) graft diameter of 1·2(0·2) mm was found at the distal anastomosis in the knitted group. There was no difference in graft patency between the groups and only one graft became infected.

Conclusion This study suggests that knitted and woven grafts have similar clinical performance and therefore the less expensive material (woven) should usually be selected unless haemorrhagic complications are anticipated.

Dacron (Du Pont, Wilmington, Delaware, USA) has been the material of choice for aortic prosthetic grafts since it was introduced in the late 1950s[1]. The original grafts were of woven construction which resulted in a small pore size and little bleeding through the graft. The development of industrial machine manufacturing led to the production of knitted grafts which, although much more porous, had the theoretical advantage of improved operative handling qualities. This was followed by the addition of a velour construction to increase tissue incorporation[2,3], and more recently by impregnation with collagen or gelatin, avoiding the necessity to 'preclot' the graft with the patient's own blood, thus reducing initial blood loss[4].

Dacron is a synthetic multifilament yarn which has to be either woven or knitted to form a sheet. Woven material, manufactured with warp and weft fibres, does not rely on looping of the yarn around a needle and the material is therefore more compact[4]. Weaving results in a low-porosity graft with greater strength and resistance to deformation compared with the looser structure of the knitted graft. The stiffness of the woven structure is thought to make it more difficult to handle and suture compared with the more elastic knitted structure. Knitted grafts behave like knitted garments which are prone to stretching, and the stability of Dacron is not as good as was originally thought[5].

Despite the theoretical advantages of coating knitted grafts with a material designed to reduce blood loss, their performance has not been directly compared with that of woven grafts in a prospective randomized trial.

The purpose of this study was to compare the graft handling qualities and operative blood loss of these two arterial prostheses. In addition, graft patency, infection rate, false aneurysm formation and patient survival at 1 year was assessed.

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Patients and methods

All patients having elective surgery for an infrarenal aneurysm or occlusive aortoiliac disease between January 1991 and August 1994 were asked to participate in this study. After obtaining informed consent patients were prospectively and randomly allocated to one of two groups using Geigy randomization tables. A woven Dacron graft (Cooley Verisoft) was used for one group while the other had a presealed knitted Dacron graft inserted (Microvel double Velour with Haemashield). Both of these grafts were manufactured and supplied by Meadox (Caddington, UK).

All patients with occlusive disease had a bifurcated graft inserted, end to side, between the upper end of the infrarenal aorta and the iliac or common femoral arteries. Patients with aneurysmal disease had either a tube graft inlayed end to end, or a bifurcated graft stretched to the iliac or femoral arteries with an end-to-side distal anastomosis and closure of the common iliac vessels, the choice being dependent on the state of the iliac arteries.

The presence of diabetes mellitus, hypertension or hyperlipidaemia and smoking habits were recorded. The intraoperative blood loss was estimated from swab weighing and measurement of the volume of blood within the suction bottle. The time taken to perform the distal anastomosis was recorded.

The patients were reviewed 1 year later when graft patency, dilatation (increase in diameter) and the presence of any myointimal hyperplasia were assessed using duplex imaging (Acuson 128 XP10; Acuson, Mountain View, California, USA). The anastomoses were displayed longitudinally and callipers placed across both graft and native artery to measure the luminal diameter. These measurements were compared with the known graft diameter at the time of insertion. The ultrasonography technician did not know the type of graft that had been inserted. An intravenous digital subtraction arteriogram was obtained if the duplex study was equivocal or if there was any suggestion of graft occlusion.

A small group of 18 patients (16 knitted and two woven tube grafts) who had initially been recruited and randomized were subsequently withdrawn when it became apparent after operation that they would not return to the UK for follow-up. There is therefore a slight imbalance between the number of knitted and woven grafts included.

Results

A total of 267 patients were entered into the trial, of which 225 (84·3 per cent) were men and 42 (15·7 per cent) women. Some 141 patients (52·8 per cent) had woven and 126 (47·2 per cent) had knitted grafts inserted. Of the 141 woven grafts 86 (61·0 per cent) were bifurcation and 55 (39·0 per cent) were tube grafts. Of the 126 knitted grafts 88 (69·8 per cent) were bifurcation and 38 (30·2 per cent) were tube grafts. Some 115 patients (43·1 per cent) had aortoiliac occlusive disease and 152 patients (56·9 per cent) had an aortic aneurysm. Mean(s.d.) age of the patients with occlusive disease was 60·4(8·4) years and of those with aneurysms was 68·8(7·7) years. The patients with occlusive disease had a mean(s.d.) claudication distance at the time of surgery of 140(96) yards.

Actual blood loss was extremely variable and ranged from 150 to 10 000 ml, but the mean(s.d.) operative blood loss was significantly greater in patients who had a woven graft inserted (1690(1424) ml) compared with those with a knitted graft (1363(1172) ml) ($P = 0{\cdot}049$, Student's *t* test).

Mean(s.d.) time taken to construct the groin anastomosis in patients who had a woven bifurcation graft was 18·8(7·5) min and 18·0(7·5) min for a knitted graft.

Ten patients died in hospital (3·7 per cent), all within 24 h of surgery. Three (1·1 per cent) died as a result of technical problems, but none related to the grafts. Ten further patients (3·7 per cent) died within 1 month of discharge (30-day mortality rate of 7·5 per cent). Another 31 patients died in the next 11 months, giving an overall 1-year mortality rate of 19·1 per cent and a remaining 216 patients potentially available for follow-up. Of these 216 patients, 187 (86·6 per cent) were contacted and rescanned but 29 (13·4 per cent) could not be traced or recalled despite stringent efforts. The cause of death given on the death certificate was available for 21 of the 31 late deaths. Ten patients had died from myocardial infarction and five from heart failure. The cause of death was not related to atherosclerosis in the remaining six.

All grafts were patent at the time of discharge. A single limb of six bifurcated grafts (2·2 per cent of all grafts) had occluded by 1 year. Three of the occluded grafts were woven and three knitted. All had been inserted for occlusive disease. No tube graft occluded and no bifurcation graft developed bilateral occlusions.

There was a mean(s.d.) reduction in diameter of the woven grafts at 1 year of 1·26(1·75) mm compared with the diameter at discharge. There was a mean(s.d.) increase in the diameter of knitted grafts at 1 year of 1·2(0·2) mm indicating a small increase in the cross-sectional area. No evidence of myointimal hyperplasia was found at 1 year at any of the distal anastomoses.

One knitted graft became infected when a graft–enteric fistula developed. This patient died 6 months after the operation. No other graft infections had occurred by 1 year.

Discussion

Manufacturers' sales suggest that woven grafts are still more popular than knitted grafts (personal communication). Various modifications have been made in both types of graft which have been claimed to improve performance but until now the two types of graft have never been evaluated in a prospective randomized study.

Double velour knitted Dacron aortic grafts have been shown to have greater anastomotic strength than woven aortic grafts in models, but both were found to be less satisfactory than an equivalent polytetrafluoroethylene graft[6]. Biophysical, histopathological and ultrastructural studies in a few grafts removed after many years have shown that the fibre structure and resistance to degradation is better in woven than knitted Dacron grafts[7].

The interlacing structure of the woven graft with parallel fibres arranged compactly at right angles to each other is much more resistant to stress than the equivalent knitted graft where the looped structure is more prone to deformation[8]. It is thought that the repetitive pulsatile pressure of arterial blood is responsible for the dilatation found in knitted grafts causing the looping nature of the knit to take up a more elliptical shape[8]. The tighter the knit the greater the resistance to deformation[5]. Modern knitted grafts may not have the dilatation problems of their predecessors. In the few retrospective studies that have compared woven and knitted grafts dilatation is the most commonly reported long-term complication of knitted Dacron bifurcation grafts. Warp-knitted grafts do not unravel, curl up, or fray at the edges when cut, unlike woven grafts[8–11], but suture line disruption, anastomotic aneurysms, holes, tears, mural thrombus, embolization, bleeding and infections are all more common[8]. Many surgeons choose knitted grafts because of their better intraoperative handling qualities.

Recent improvements in woven grafts, including those used in this study, have eliminated unravelling and reduced the problems of fraying by using an interlocking stitch. Graft pliability has been increased by the use of three low-twist yarns and a loose crimp. Pseudointima fixation may be improved by the addition of an internal velour surface[12].

The condition of knitted and woven Dacron aortoiliac grafts has been assessed retrospectively using computed tomography[13]. Knitted grafts were found to dilate most in the first year with only marginally greater increases in diameter at 5 years. The mean dilatation of the main trunk of a knitted graft was 34 per cent after 5 years compared with 15 per cent for a woven graft. The limb dilatation was 42 per cent for the knitted compared with 25 per cent for the woven. Some 9 per cent of the knitted grafts developed a proximal anastomotic dilatation compared with 2 per cent of the woven grafts[13].

In a small study recently performed in this unit it was found that grafts were all within 1 mm of manufactured size when assessed by duplex imaging immediately after insertion. Nothing like the amount of dilatation was found in the knitted grafts inserted in the present study after 1 year and this may reflect improved manufacturing technology. Woven grafts do not dilate and the present study demonstrated only a small reduction in diameter without any loss of patency.

There was no appreciable difference in the time taken to perform the groin anastomoses for either graft, which suggests that there is little difference in their handling properties. Only one patient developed a graft infection.

This very low infection rate makes a single-centre study to investigate the relative risk of graft infection in the two groups totally impracticable.

Collagen impregnation of a knitted graft reduces the intraoperative blood loss and avoids the time-consuming process of preclotting. The collagen-impregnated knitted grafts used in this study had a small but significant reduction in mean blood loss in comparison to their woven equivalents. The clinical benefits were small, saving approximately one unit of blood per patient. This advantage would have been negated had the woven graft been collagen impregnated. Such a graft is now available.

Myointimal hyperplasia develops at the anastomoses of both polytetrafluoroethylene and Dacron grafts and has hampered the development of small diameter prosthetic grafts by causing stenosis and occlusion[14]. Myointimal hyperplasia develops with equal frequency in woven and knitted Dacron grafts implanted as different limbs of composite aortobifurcation grafts in animal models[15]. Duplex imaging in the present study was unable to detect myointimal hyperplasia by 1 year in either type of graft.

Grafts inserted for aneurysmal disease are known to have a better patency than those inserted for stenosing disease[16]. Graft occlusions occur almost exclusively in single limbs of bifurcation grafts inserted for aortoiliac occlusions and often develop in the first 100 postoperative days[16]. Up to 12 per cent of graft limbs occlude by 5 years[8], and this may represent a low estimate of the true figure. A 15-year follow-up of patients who had aortobifemoral Dacron grafts inserted for occlusive disease showed that only 25 per cent of patients survived and only 20 per cent still had both graft limbs patent[17].

No overall difference in the patency of woven and knitted grafts was found in a small retrospective study of 79 patients[18]. In the present study six early unilateral graft limb occlusions were detected with three in each of the woven and knitted groups. This is too small a number to justify any comparison between the two graft types but an overall occlusion rate of 2·2 per cent at 1 year was lower than expected.

Patients having aortoiliac surgery have a reduced life expectancy. The mortality rate in this study of just under 20 per cent at 1 year is comparable to other reports[4,16,19]. The high mortality rate at 1 year combined with the low occlusion and infection rates have reduced the power of this study to detect minor differences in these complication rates and a large randomized multicentre study would be required to show a significant difference.

The results of the present study do not support the view that bifurcated prostheses made of knitted and impregnated Dacron have better patency or lower infection rates than their woven Dacron equivalents. As the intraoperative and postoperative performances are so similar it is more appropriate to consider the price of the two grafts. In the UK at present a non-impregnated woven prosthesis costs approximately half the price of the knitted alternative manufactured by the same company, and should therefore be the graft of first choice.

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Results of aortic screening in the brothers of patients who had elective aortic aneurysm repair

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Background Brothers of patients with an abdominal aortic aneurysm (AAA) are at high risk. In the present study brothers of patients who underwent elective AAA surgery were invited for aneurysm screening and the psychological consequences studied.

Methods All brothers over the age of 50 years were invited for abdominal ultrasonography. They were asked to complete a standard psychological well-being questionnaire both before, and 3 months after screening.

Results Some 571 brothers were identified: 251 were dead, 35 lived abroad, 16 could not be contacted for other reasons, 46 refused to participate and 13 were already known to have an AAA. Some 210 subjects (37·8 per cent) accepted the offer of screening. A new AAA was detected in 26 (12·3 per cent, 95 per cent confidence interval 8–18 per cent) of the men screened resulting in an overall prevalence of 18 per cent (95 per cent confidence interval 13–26 per cent). Eight (3·8 per cent) aneurysms were 5 cm or more in diameter and elective surgery was performed in five patients (2·4 per cent). The psychological dimensions of well-being (depression, anxiety, energy, and positive well-being) had not changed significantly 3 months after screening.

Conclusion The prevalence of AAA in brothers of patients with AAA is far higher than in the overall male population of the same age. Screening does not seem to have a negative influence on psychological well-being.

The overall mortality rate following ruptured abdominal aortic aneurysm (AAA) is over 80 per cent[1]. The risk of death associated with elective aortic surgery is approximately 5 per cent[2,3]. Screening may be a way of reducing total mortality from ruptured AAA. Ultrasonographic imaging of the aorta is cheap, and sensitivity and specificity rates are estimated to exceed 95 per cent[4,5]. Aortic diameter can be measured within a detection range of less than 2·2 mm[6]. The estimated prevalence of AAA within a random sample of 65–74-year-old men is 3–6 per cent[7]. To increase the yield of a screening programme, identification of subgroups known to have a higher prevalence of AAA has been proposed[7,8]. Several studies have shown a clear familial aggregation of AAA. Prevalence rates of 19–29 per cent in brothers have been reported[9–14]. Several aspects of screening need to be studied before screening for AAA in brothers is introduced[15]. In a prospective multicentre study the yield of a targeted screening programme for brothers of patients who had elective AAA surgery was investigated and the psychological consequences of screening were studied.

Patients and methods

The study involved the brothers of 291 patients (261 men and 30 women) admitted to five hospitals in the Netherlands between 1 May 1993 and 1 May 1995 for elective infrarenal AAA surgery. In the district hospitals of St Antonius Hospital in Nieuwegein and the Westeinde Hospital in the Hague, 116 and 36 patients underwent aortic surgery respectively. In the University Hospitals of Utrecht, Maastricht, and Leyden, 68, 38, and 33 operations were performed respectively. Mean(s.d.) age of the patients was 69(8) (range 45–87) years. All patients were requested to supply age, vital status, and address of any brothers. Consent for contacting the brothers was also requested.

Brothers who were still alive and 50 years of age or older were contacted by telephone and provided with information regarding the study. They were invited for ultrasonography of the abdominal aorta in a hospital near their home. They were asked to complete general health and well-being questionnaires. In the general health questionnaire, information pertaining to the following items was registered: smoking habits, previous myocardial and cerebral infarction, use of antihypertensive drugs and diabetes mellitus. The well-being questionnaire was psychological in nature (translated into Dutch) aimed at assessing the influence of screening on the four dimensions of depression, anxiety, energy, and positive well-being. It contained six items for depression, six for anxiety, four for energy and six for positive well-being. Higher total and domain scores indicated better psychological well-being. The validity[1] and reproducibility of this self-reported questionnaire is good[16].

Three months after ultrasonography the participants were asked once again to complete the well-being questionnaire. Results of the ultrasonography were sent to the trial office by general practitioners. An AAA was defined as a localized aortic dilatation with an anteroposterior diameter of 30 mm or more, or 1·5 times the proximal aortic diameter[17]. Two measures were calculated: the new detection rate and the overall prevalence comprising newly detected AAAs and the AAAs already known. Differences between subgroups were tested using χ^2 test. Mean scores of well-being and the subdomains were compared using

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the paired *t* test. The study was approved by the medical ethics committees of all participating centres.

Results

Collectively, the 291 patients who underwent elective AAA repair had 603 brothers. Of this total, 32 were under 50 years of age, 251 had died, and 16 could not be contacted because the original patient had not provided a recent address. Of the remaining 304 brothers, 269 were judged eligible for the study. Of these, 46 refused screening (generally because of health problems). Thirteen individuals were already known to have an AAA and were also not included in the study. Some of them had already had AAA repair. Some 210 brothers (79 per cent of those eligible) participated in the study and underwent abdominal ultrasonographic imaging.

An AAA was detected in 26 brothers. The new detection rate was 12·3 per cent (95 confidence interval (c.i.) 8–18 per cent) and the overall prevalence rate (26 plus the 13 AAA already known) was 18 per cent (95 per cent c.i. 13–23 per cent). Mean(s.d.) diameter of the aneurysms was 4·2(1·4) cm, the median was 3·4 cm (25th percentile 3·0 cm, 75th percentile 5·1 cm). In 15 men the AAA was smaller than 4 cm. In eight (3·8 per cent) the AAA was 5 cm or more. Five of these had aortic aneurysm repair. Seven men are included in a follow-up schedule, four died from other illnesses during follow-up. Follow-up was not considered necessary by the participating surgeons in the remaining ten men who were elderly, suffered from comorbidity and had a relatively small AAA.

Brothers with an AAA were older than brothers without an AAA (mean difference 3·5 years), and more commonly had a history of myocardial infarction ($P = 0{\cdot}04$), transient ischaemic attack or stroke ($P = 0{\cdot}09$) (*Table 1*). A total of 174 (83 per cent) of the participants in the study completed the well-being questionnaire before, as well as three months after the ultrasonographic scan (*Table 2*). There were no significant differences either in the total well-being sum-score ($P = 0{\cdot}8$) or in the scores of the different domains.

Table 1 Characteristics of brothers with and without abdominal aortic aneurysm

Characteristics	All brothers* ($n = 210$)	Brothers without AAA ($n = 180$)	Brothers with AAA ($n = 26$)
Age (years)			
50–59	60 (29)	55 (31)	4 (15)
60–69	96 (46)	83 (46)	12 (46)
70–79	47 (22)	37 (21)	8 (31)
80 +	7 (3)	5 (3)	2 (8)
Cardiac disease	64 (31)	54 (30)	9 (35)
Myocardial infarction	29 (14)	22 (12)	7 (27)
Angina	38 (18)	33 (18)	4 (15)
Arrhythmia	20 (10)	16 (9)	4 (17)
Hypertension	24 (11)	20 (11)	3 (12)
Minor stroke and TIA	12 (6)	7 (4)	3 (12)
Diabetes mellitus	16 (8)	12 (7)	4 (15)
Smoking	69 (33)	61 (34)	7 (27)

Values in parentheses are percentages. *Results of ultrasonography were not available for four brothers. AAA, abdominal aortic aneurysm; TIA, transient ischaemic attack

Table 2 Total well-being score before and after aortic screening*

	Before screening	After screening
Total score for well-being	53(12·1)(0·9)	53·2(12·4)(0·9)
Subscales		
Depression	3·4(4·2)(0·3)	3·2(3·9)(0·3)
Anxiety	3·0(3·6)(0·3)	3·4(4·8)(0·4)
Positive well-being	14·2(4·2)(0·3)	14·4(4·6)(0·4)
Energy	9·2(2·9)(0·2)	9·4(3·1)(0·2)

Values are mean(s.d.)(s.e.m.)

Discussion

One-third (210 of 603) of the brothers initially identified were screened for an AAA. The mean age (69 years) of the index patients was relatively high and a significant number of their brothers had died. The prevalence of AAA in the study (18 per cent) was higher than in the overall male population of the same age (3–6 per cent)[7]. Prevalences of between 13 and 29 per cent have been reported in other studies[9,11–14]. Except in the case of one study, where no definition of AAA was provided, researchers applied size definitions similar to this study. The present study differed in that it was limited to brothers 50 years of age and older. The research conducted by Adamson *et al.*[11] also included younger brothers with correspondingly higher prevalence, which may be a chance finding. Thirteen brothers, a relatively high number, had already had aneurysms diagnosed. In a community which had not been so well monitored medically these previously diagnosed AAA would have been discovered only by deliberate sibling screening. In the Netherlands it is common for patients to ask their surgeon about the risk to their siblings.

The compliance rate in this study was remarkably high (210 of 269) in comparison to attendance rates in cervical cancer and breast cancer screening programmes. The siblings of AAA patients are much older than the women invited for breast and cervical cancer screening programmes. Having a sibling who has had a complicated operation for an AAA appears to be a factor influencing attendance. Another difference in this screening programme was the means used to issue the invitation. The first telephone contact with the brothers allowed for many questions to be answered, which would not have been possible if invitations had been sent by mail. Invitations by telephone are time-consuming but seem to be worthwhile.

Brothers of aneurysm patients have a high prevalence of aortic aneurysms and, until national population aneurysm screening programmes can be agreed, such targeted screening is worthwhile.

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Role of saphenous vein surgery in the treatment of venous ulceration

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Background This paper describes local anaesthetic saphenous disconnection in elderly patients for the treatment of venous ulceration in legs with either saphenous venous reflux alone or in combination with deep venous reflux.

Methods Ambulatory venous pressure was measured in 16 legs with saphenous vein reflux alone and in nine legs with combined deep and saphenous venous reflux before, immediately after and 3 months after saphenofemoral or popliteal disconnection. Ulcer area was measured by computerized planimetry before surgery and at 1 and 3 months after operation. No compression bandages or hose were applied after surgery unless the ulcers had not begun to heal after 1 month.

Results In legs with saphenous reflux alone all ulcers healed without compression bandages at a median of 81 (range 14–253) days and the pressure relief index (PRI) improved significantly both after surgery and at follow-up. None of the ulcers in the nine limbs with saphenous and deep venous reflux healed without compression bandaging and the PRI was unchanged immediately following surgery and at follow-up.

Conclusion Saphenous vein disconnection improves venous function and heals venous ulcers without compression bandaging if the deep veins are normal. This procedure under local anaesthetic may be particularly suitable for elderly patients, but long saphenous vein stripping should be added in young patients.

Venous ulceration results from prolonged venous hypertension[1]. In up to 57 per cent of cases this is due to saphenous vein reflux alone but in up to 32 per cent of cases there is, in addition, deep vein reflux[2]. The role of surgical correction of saphenous vein reflux as a therapeutic manoeuvre in the treatment of venous ulceration has previously been disregarded[3,4]. Darke and Penfold[5] have demonstrated that saphenous vein ligation with stripping to the knee (combined with postoperative compression in one-third of cases) results in ulcer healing if the deep veins are normal, with associated improvement in ambulatory venous pressure[6]. Controversy exists regarding the role of saphenous vein surgery when there is co-existing deep venous reflux. Scurr[7] has advocated saphenous vein surgery in this situation, whereas Mayberry *et al.*[8] consider that this approach is unproven. The principle behind the treatment of venous ulceration is to reduce venous hypertension, and therefore stripping of the saphenous vein may not be mandatory. All previous reports have included saphenous vein stripping and/or postoperative compression therapy in addition to saphenous vein disconnection. The aim of this study, therefore, was to examine the safety and efficacy of local anaesthetic day-case saphenofemoral or popliteal disconnection without stripping the saphenous vein or use of postoperative compression in ulcerated limbs with isolated saphenous venous reflux and in those with combined deep and saphenous venous reflux.

Patients and methods

Patients with active leg ulceration were identified from those attending a venous ulcer assessment clinic[2]. Ulcers were defined as venous if the only demonstrable abnormality was venous reflux of more than 0·5 s duration with an ankle : brachial systolic pressure index of over 0·9.

The study was designed to investigate the role of local anaesthetic saphenofemoral and/or saphenopopliteal disconnection in a total of 40 legs, 20 with superficial reflux only and 20 with superficial and deep reflux. The study received local ethics committee approval. Patients had preoperative colour duplex scanning and ambulatory venous pressure (AVP) measurements recorded; these were repeated immediately after surgery (within 1 h) and at 3 months[9,10]. Venous ulcer size was measured before surgery and at 1 and 3 months after surgery. Patients were followed up for 24 months.

To assess whether the final AVP was influenced by not stripping the saphenous vein the difference between the preoperative and follow-up AVP (expressed as a percentage of the resting pressure) in legs with normal deep veins was examined and compared to the status of the saphenous vein remnant at follow-up. Each leg was classified into one of two groups. Group 1 included legs with thrombosed and/or competent saphenous veins, and group 2 included legs with reflux still present in the venous remnant. Legs that required surgery to both the long saphenous vein (LSV) and short saphenous vein (SSV) were included in group 1 only if both venous remnants were either competent or thrombosed.

Measurement of ambulatory venous pressure

AVP was measured in the standard manner[9] immediately before and after surgery i.e. within 1 h and at a 3-month follow-up visit.

From the pressure tracing obtained the resting venous pressure (RVP) (mmHg), AVP (mmHg) and time (s) to return to 90 per cent of the resting pressure (RT90) were measured. These data allowed the calculation of an overall assessment of venous calf pump function, the pressure relief index (PRI)[10].

Colour duplex imaging

A colour duplex scan of the deep and superficial veins was performed before surgery and at follow-up visit. Venous reflux was defined as the presence of reversed blood flow for more than

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0·5 s on release of a calf squeeze distal to the segment of vein under examination.

Ulcer area

Ulcer areas were determined by computerized planimetry from tracings of the ulcer perimeter before surgery and at 1 and 3 month follow-up. Healing was determined by inspection and deemed to be complete if full re-epithelialization had occurred.

Surgery

Saphenous disconnections were performed under local infiltration anaesthesia. Reflux at the saphenofemoral junction (SFJ) was treated by flush ligation of the SFJ with formal exploration, identification, ligation and division of all tributaries. Saphenopopliteal reflux was treated by flush ligation and division of the saphenopopliteal junction (SPJ). After surgery the ulcers were dressed with a simple non-adherent dressing (Johnson and Johnson, Ascot, UK), a layer of gauze, and a graduated below-knee Tubigrip (Seton Health Care Group, Manchester, UK). If after 1 month healing had not commenced this was replaced by a four-layer compression bandage.

Statistics

Data were analysed using non-parametric paired testing (Wilcoxon matched pairs) and unpaired (Mann–Whitney *U* test) as appropriate.

Results

Patients

The study was terminated after 25 legs (24 patients) had been studied because of the poor outcome in legs with combined superficial and deep reflux. Sixteen legs had isolated saphenous vein reflux distributed as follows: LSV only, nine; SSV only, four; and LSV and SSV combined, three. Nine legs had venous reflux in the deep and long saphenous systems combined; five had duplex evidence of previous deep vein thrombosis. Deep venous reflux was present throughout the full length of the superficial femoral and popliteal veins into the calf veins in all nine legs. Patients' ages, initial ulcer area and duration at the time of surgery are given in *Table 1*.

Eighteen legs had saphenofemoral disconnection, four saphenopopliteal disconnection and three had both. All patients who had saphenopopliteal disconnection had preoperative marking of the SPJ by colour duplex imaging

Ulcer healing

All 16 ulcers in legs with isolated saphenous vein reflux began to heal within 1 month of surgery, and all healed completely at a median of 81 (range 14–253) days. None required compression bandaging.

Table 1 Characteristics of the patients and ulcers

	Initial ulcer area (cm^2)	Ulcer duration before surgery (years)	Patient age (years)
Saphenous reflux only ($n = 16$)*	9 (3–14)	2 (1–6)	73 (56–77)
Deep and superficial reflux combined ($n = 9$)*	18 (9–92)	2 (1–3)	77 (63–85)
P†	0·02	0·59	0·41

*Values are median (range). †Mann–Whitney *U* test

None of the nine ulcerated legs with combined deep and saphenous vein reflux had started to heal by 1 month. Median ulcer area had increased from 18 (range 9–92) cm^2 to 24 (15–126) cm^2 ($P = 0{\cdot}01$, Wilcoxon matched pairs). All nine legs were subsequently treated with four-layer compression bandaging. After a median follow-up of 16·5 (range 10–24) months, three ulcers had healed at 136, 168 and 196 days. The remaining six were unhealed.

Venous function

The PRI (*Fig. 1*) increased significantly immediately after surgery and at follow-up visit in legs with isolated saphenous reflux. In legs with deep and saphenous reflux combined the PRI remained unchanged immediately after surgery and at follow-up visit.

The RT90 (*Fig. 2*) lengthened significantly immediately after surgery in legs with isolated saphenous reflux. This lengthening in the RT90 was maintained but not improved at follow-up visit. In legs with combined deep and saphenous reflux there was no change in the RT90 after surgery or at follow-up visit.

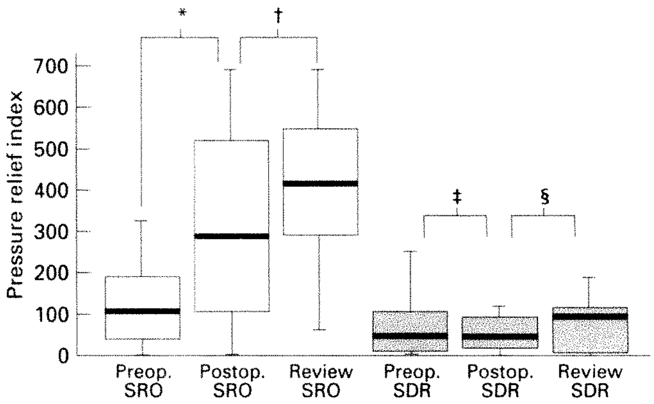

Fig. 1 Pressure relief index before and after surgery and after 3 months. SRO, saphenous reflux only; SDR, saphenous and deep reflux combined. Bars, median; box, interquartile range; whiskers, range. *$P = 0{\cdot}001$; †$P = 0{\cdot}04$; ‡$P = 0{\cdot}58$; §$P = 0{\cdot}25$ (Wilcoxon matched pairs)

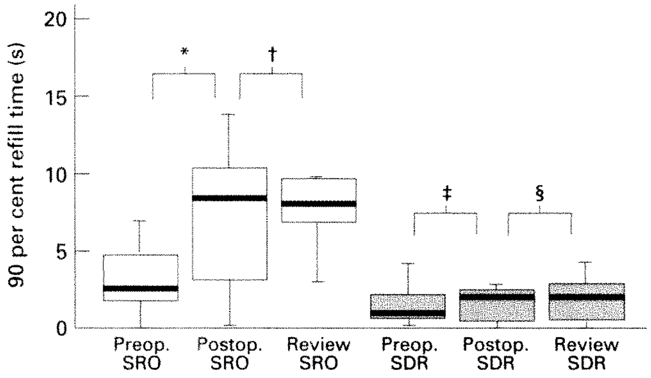

Fig. 2 Ninety per cent refill time before and after surgery and after 3 months. SRO, saphenous reflux only; SDR, saphenous and deep reflux combined. Bars, median; box, interquartile range; whiskers, range. *$P = 0{\cdot}003$; †$P = 0{\cdot}27$; ‡$P = 0{\cdot}80$; §$P = 0{\cdot}42$ (Wilcoxon matched pairs)

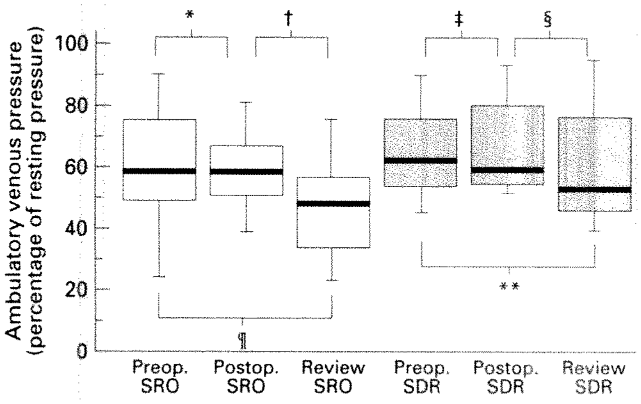

Fig. 3 Ambulatory venous pressure (as a percentage of resting pressure) before and after surgery and after 3 months. SRO, saphenous reflux only; SDR, saphenous and deep reflux combined. Bars, median; box, interquartile range; whiskers, range. *$P = 0{\cdot}55$; †$P = 0{\cdot}003$; ‡$P = 0{\cdot}44$; §$P = 0{\cdot}35$; ¶$P = 0{\cdot}001$; **$P = 0{\cdot}61$ (Wilcoxon matched pairs)

The AVP (*Fig. 3*) was unchanged after surgery in legs with saphenous reflux only but at follow-up visit had significantly decreased. The AVP remained unchanged throughout the study in legs with combined deep and saphenous reflux.

Distribution of venous reflux at follow-up

Of the 16 legs with isolated saphenous vein reflux, 12 LSVs and seven SSVs were ligated. At follow-up visit all 12 LSVs had been disconnected adequately at the SFJ and of the unstripped remnants, five had thrombosed, three remained incompetent, three had become competent and one LSV was not visualized fully. Of the seven SSV ligations, all had been disconnected, two SSV remnants had thrombosed, three regained competency, one remained incompetent and one was found to have a recurrent connection with the deep venous system. All of the deep veins in this groups of limbs remained fully patent and competent.

Median difference in preoperative and follow-up AVP in those limbs with normal deep veins was as follows: group 1 (thrombosed or competent LSV or SSV) 16·5 (range 5–37) per cent and group 2 (incompetent LSV or SSV) 10 (range −2 to 30) per cent ($P = 0{\cdot}44$, Mann–Whitney U test).

Considering legs with combined deep and saphenous venous reflux, all nine LSVs were adequately disconnected at the SFJ and all deep veins remained patent and incompetent. The states of the LSV remnants were: four thrombosed, three remained incompetent, one had recurrent reflux from the groin and one was visualized inadequately. None had regained their competency.

Discussion

This study examined the efficacy of saphenofemoral and/or popliteal disconnection alone without stripping the saphenous vein and without postoperative compression. This is important for three reasons. First, if correction of venous hypertension is of prime importance in achieving ulcer healing, then stripping the LSV may be unnecessary. Second, saphenous disconnection alone lends itself to local anaesthetic day-case surgery and does not carry the morbidity of LSV stripping. Third, postoperative compression was avoided which allowed full evaluation of the surgical procedure itself.

In the absence of deep venous reflux, saphenous disconnection alone results in healing without the need for compression hose or bandages. This was accompanied by an improvement in the PRI in the immediate postoperative phase and a further improvement 3 months following surgery. The parameters that constituted the PRI behaved differently. The RT90 lengthened immediately after operation and although this was maintained at 3 months it did not improve further. The AVP, however, failed to improve immediately after surgery but at follow-up was significantly lower than either the preoperative or the postoperative value. This supports a theory of volume overload[11,12] on the calf muscle pump in that saphenous disconnection immediately removes the source of venous reflux (reflected in the lengthening of the RT90) but it takes time for the AVP to drop to a significantly lower value. This suggests that for the calf muscle pump to regain its function, some degree of recovery and accommodation to the reduced reflux load is required, hence the delay in obtaining a reduced AVP. It is also noteworthy that three of the seven LSV remnants regained their competence suggesting that reducing the refluxing volume allows the veins to regain their tone, allowing opposition of vein valve cusps.

The haemodynamic changes demonstrated by this study suggest that saphenous vein stripping is unnecessary to achieve ulcer healing and improved venous function if the deep veins function normally. There was no detrimental haemodynamic effect of leaving a refluxing LSV remnant behind. However, it has been shown that the incidence of recurrent reflux at the SFJ[13] is greater if the SFJ is disconnected without stripping. Although the patients in this study were elderly, many venous ulcers begin in young patients who require a durable surgical procedure to minimize venous reflux recurrence and hence ulcer recurrence. In younger patients with venous ulceration and isolated saphenous reflux saphenous disconnection and stripping under general anaesthesia is the preferred option. The data presented here are drawn from a small number of patients; the durability and effect on ulcer recurrence rates need further evaluation.

It has been recommended that in the presence of coexisting deep reflux, saphenous reflux should be corrected as far as possible for venous ulceration[7]. In this study saphenous disconnection had no effect on ulcer area or venous haemodynamics in legs with combined deep and saphenous vein reflux.

Local anaesthetic, day-case saphenous disconnection is safe in the elderly. Providing the deep veins were normal, all ulcers in this study healed without postoperative compression. If deep venous reflux extended below the knee, saphenous disconnection had no effect on venous haemodynamics and all ulcers failed to heal without compression.

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Lower limb ischaemia–reperfusion injury causes endotoxaemia and endogenous antiendotoxin antibody consumption but not bacterial translocation

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Background It has been suggested that reperfusion of the acutely ischaemic lower limb alters gut permeability. The effect of lower limb ischaemia–reperfusion on systemic endotoxin and antiendotoxin antibody concentrations and the incidence of bacterial translocation was investigated.

Methods Systemic endotoxin and antiendotoxin antibody concentrations were measured in five groups of male Wistar rats: control, after 3 h of bilateral hind limb ischaemia alone, and after 3 h of bilateral hind limb ischaemia followed by 1, 2 or 3 h of reperfusion. A second experiment examined translocation of indigenous bacteria following 2 h of reperfusion in a similar model.

Results Ischaemia followed by reperfusion for 1, 2 or 3 h caused a significant increase in plasma endotoxin concentration to mean(s.e.m.) 10·0(3·0), 44·8(19·2) and 20·2(6·2) pg/ml compared with that in control animals (2·58(0·91) pg/ml) or animals in the ischaemia alone group (1·2(0·9) pg/ml) ($P < 0{\cdot}05$). This was associated with a significant reduction in endogenous antiendotoxin antibody (immunoglobulin (Ig) G and IgM) concentration. No significant bacterial translocation was detected in any of the groups studied.

Conclusion These results demonstrate that a remote and isolated ischaemia–reperfusion injury to the lower limb, in the absence of infection or bacterial translocation, causes endotoxaemia. Further studies are needed to evaluate the role of endogenous antiendotoxin antibodies in this situation.

Multiple organ dysfunction syndrome (MODS) is a significant cause of morbidity and death after trauma and major vascular surgery such as abdominal aortic aneurysm surgery[1–3]. Until recently it was generally accepted that MODS was a complication of uncontrolled infection or a manifestation of an occult septic focus, but it is now clear that MODS can develop in the absence of infection[4,5]. The development of sepsis syndrome and MODS in patients after trauma, major surgery or critical illness in the absence of an identifiable focus of infection has lead to the hypothesis that micro-organisms from the intestinal lumen may be the source of bacteria and that endotoxin is involved in the pathogenesis and pathophysiology of these syndromes[6].

The gastrointestinal tract is normally inhabited by a large collection of microbial species and high concentrations of endotoxins[7,8]. To protect the host from being invaded by its own flora or their toxins the gut is equipped with efficient defence mechanisms which constitute 'the gut barrier'. These include a normal ecological balance of gastrointestinal microflora that competitively inhibit overgrowth, and hence translocation, of any particular species and an intact intestinal mucosa that provides a physical barrier to translocation of particles including antigens and bacteria[9]. Immune defences such as gut-associated lymphoid tissue, Kupffer cells of the liver and serum immunoglobulins act as a second line of defence should breach of the physical barrier occur[10]. It has been suggested that circulating endogenous antiendotoxin antibodies can bind and neutralize endotoxin escaping from the gut. This was demonstrated by a decrease in their plasma concentration following exposure to endotoxin[11]. Serum immunoglobulins can also opsonize translocating bacteria to increase their clearance from lymphoid organs and the bloodstream thereby decreasing their systemic dissemination[12].

Clinical studies have suggested that gut permeability is altered following major vascular surgery and endotoxin has been demonstrated in plasma of patients undergoing abdominal aortic aneurysm replacement[13,14]. The link between lower limb ischaemia–reperfusion injury, gut permeability and the development of remote organ dysfunction following abdominal aortic aneursym surgery is unclear. The objectives of this study were to determine the effect of ischaemia–reperfusion injury of the lower limb on systemic endotoxin and endogenous antiendotoxin antibody concentrations, and bacterial translocation in a rodent model.

Materials and methods

Animal model

Adult male Wistar rats weighing 300–350 g obtained from a breeding colony were used in the study. Animals were kept under standard conditions and had free access to standard rat chow (R. Morton, Ballymena, UK) and water *ad libitum* until the morning of the experiment. The animals were anaesthetized with subcutaneous ketamine 80 mg/kg and xylazine 8 mg/kg. Hydration of the animals was maintained by injection of sterile 0·9 per cent sodium chloride (Antigen Pharmaceuticals, Roscrea, Ireland) 3 ml per kg per h subcutaneously. Using a heating lamp, body temperature was kept at 37°C. Bilateral hind limb ischaemia was induced by applying rubber band tourniquets high

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around each thigh as described originally by Rosenthal[15]. At the end of the ischaemic period reperfusion of the limbs was achieved by releasing the tourniquets. All procedures involving animals were carried out in accordance with the regulations of the United Kingdom Animals (Scientific Procedures) Act, 1986.

Experiment 1

Blood samples were taken from five groups of animals (12 in each group): control (6 h of general anaesthesia) (group 1); after 3 h of bilateral hind limb ischaemia alone (group 2); and after 3 h of bilateral hind limb ischaemia followed by reperfusion for 1, 2 or 3 h (groups 3, 4 and 5) (*Fig. 1*).

Blood sampling. At the time of blood sampling the chest wall was cleansed with chlorhexidine in spirit, a 1-cm disc of skin was excised and a butterfly needle connected to a 10-ml syringe was then used to obtain a blood sample by direct cardiac puncture. Blood samples were collected into heparinized (20 units per ml blood) sterile pyrogen-free tubes. Samples were immediately transferred on ice to be centrifuged at 200 r.p.m. (at 4°C) for 10 min. Plasma was then aliquoted into sterile cryotubes (Nunc; Intermed, Roskidle, Denmark) and stored at −70°C until the time of assay for endotoxin and antiendotoxin antibody.

Endotoxin assay. Bacterial endotoxin was quantified in duplicates using an endpoint chromogenic Limulus Amoebocyte Lysate assay (Quadratech, Epsom, UK). Samples were diluted (1:10 with sterile pyrogen-free water and heat-treated at 75°C for 10 min to remove plasma inhibitors. The concentration of endotoxin in the samples was calculated from a standard curve which was generated in 10 per cent normal rat plasma using *Escherichia coli* endotoxin (0111:B4) supplied with the kit and similarly treated. The amount of endotoxin in the sample was determined photometrically at 405 nm. The assay had a sensitivity of 8·3 pg/ml and range of 8·3–100 pg/ml. Each aliquot was assayed for endotoxin only once. If the assay gave poor duplicates or high values, which may indicate contamination, a fresh aliquot of the same sample was tested. The interassay and intra-assay coefficients of variation were less than 10 per cent and less than 15 per cent, respectively. The assay was always undertaken by the same individual who was specifically assigned to measuring endotoxin.

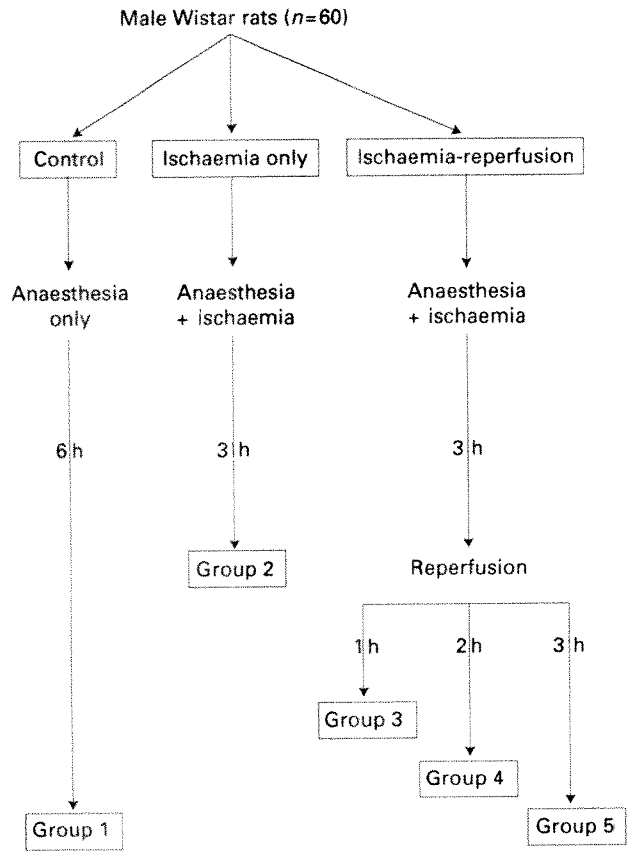

Fig. 1 Experimental design

Antiendotoxin antibody assay. The 'EndoCAb' enzyme-linked immunosorbent assay, which measures antibody levels to the core glycolipid region of lipopolysaccharide, was used to measure antiendotoxin antibody levels[16]. The microplates (G.R. Barclay, Scottish Blood Transfusion Centre, Edinburgh, UK) were previously coated with a 'cocktail' of core lipopolysaccharide from rough mutants of a number of bacteria complexed with polymyxin and then blocked with 5 per cent bovine serum albumin. Plasma samples were diluted 1:200 using phosphate buffered saline, pH 7·4 containing 0·05 per cent Tween (Sigma, Poole, UK), 0·5 per cent bovine serum albumin (Sigma) and 4 per cent polyethylene glycol (BDH Chemicals, Poole, UK). A normal plasma dilution curve was obtained by using plasma at a range of dilution from 1:50 to 1:1600. Standards and samples were added in duplicate to the plate at 100 μl per well. The plate was incubated for 1 h at room temperature with continuous shaking. A 1:250 dilution of the antirat immunoglobulin (Ig) G peroxidase or 1:500 dilution of the antirat IgM peroxidase (Serotec, Oxford, UK), prepared in the above diluent, was then added to each well (100 μl) for 1 h at room temperature with continuous shaking. Following this, 100 μl 3,3,5,5 tetramethylbenzidine substrate (Sigma) was added to each well for 10 min and the reaction stopped using sulphuric acid 2 mol/l. The plate was then read on a Thermomax kinetic reader (Molecular Devices, Crawley, UK) at an absorbance of 450 nm and the results calculated as a percentage of the normal range.

Experiment 2

Bacterial translocation was studied in three groups of animals: group 1, control ($n = 5$); group 2, 3 h of bilateral hind limb ischaemia alone ($n = 8$); and group 3, 3 h of bilateral hind limb ischaemia followed by 3 h of reperfusion ($n = 8$).

Collection of samples. The fur of the anaesthetized animal was cleansed with chlorhexidine and a midline laparotomy was performed. A peritoneal swab was taken to check for contamination. Using aseptic techniques the following samples were taken: (1) portal blood sample from the portal vein, (2) systemic blood sample from the inferior vena cava, (3) mesenteric lymph nodes, (4) spleen and (5) liver. These were collected into prereduced nutrient broth and the weight of each tissue sample was noted.

Peritoneal swabs. Swabs were plated out on blood, chocolate and MacConkey agar (Oxoid-Unipath, Basingstoke, UK) for aerobic culture and prereduced blood agar for anaerobic culture. They were also placed in cooked meat broth (Gibco Life Technologies, Paisley, UK) for 24 h at 37°C before plating out for aerobic and anaerobic culture as above. If the peritoneal swab was positive the animal was considered to have been contaminated and was excluded from the study.

Tissue samples. Tissue samples were homogenized in 2 ml nutrient broth and 0·1-ml aliquots of homogenate were cultured anaerobically on prereduced blood agar and aerobically on blood, chocolate and MacConkey agar. All aerobic plates were incubated for 48 h at 37°C and anaerobic plates were incubated for 5 days in an anaerobic cabinet at 37°C (Concept 300 Anaerobic Workstation; Ruskin Technology, West Bradford, UK). A 0·1-ml aliquot was also placed into cooked meat broth (Gibco) for 24 h at 37°C. This was then plated out and cultured aerobically and anaerobically as above. All plates were read and positive cultures were Gram-stained and identified using standard bacteriological techniques.

Blood cultures. Blood cultures were processed using the Bac-T/Alert blood culture system (Organon Teknika, Durham, North Carolina, USA). This is a sensitive and reliable automated system which can rapidly detect most micro-organisms[17,18]. Any positive cultures were plated out on the appropriate aerobic or anaerobic media as described above.

Micro-organism quantitation. The number of micro-organisms per gram of tissue was calculated using the formula

$$\frac{n \times 2 \times 10}{w}$$

where n is the number of colonies isolated, multiplied by 2 for the 2 ml of nutrient broth and 10 for the 0·1-ml inoculum, and w is the weight of tissue in grams.

Statistical analysis

Results are expressed as mean(s.e.m.). Kruskal–Wallis analysis of variance was used to detect differences between groups and statistical comparisons were made using the Mann–Whitney U test with a level of significance of $P < 0·05$.

Results

Plasma endotoxin concentration

No significant concentrations of endotoxin were detected in the plasma of controls or animals in the ischaemia alone group. Plasma endotoxin concentrations increased significantly in animals subjected to ischaemia followed by reperfusion compared with those in controls or animals in the ischaemia alone group ($P < 0·05$) (*Table 1*). Significantly higher concentrations of endotoxin were detected in the majority, but not all, of the reperfused animals which accounted for the high standard error of the mean observed.

Plasma antiendotoxin antibody concentration

A significant decrease in plasma concentrations of antiendotoxin antibody IgG and IgM was observed in animals following 3 h of ischaemia alone compared with those in control animals ($P < 0·05$). Plasma concentrations of both IgG and IgM antiendotoxin antibodies decreased significantly in animals subjected to ischaemia followed by reperfusion compared with those in controls ($P < 0·05$) (*Table 2*).

Bacterial translocation

Peritoneal swabs were sterile in all samples. No evidence of bacterial translocation was detected in any animal in the control group. Bacterial translocation occurred to mesenteric lymph nodes and liver in one animal in the ischaemic group (Gram-positive bacilli) and to the mesenteric lymph nodes in one animal in the ischaemia–reperfusion group (Gram-positive bacilli and coagulase-negative staphylococci). No bacterial growth was detected in the portal or the systemic blood in any group.

Discussion

The findings in this study concur with previous observations that ischaemia–reperfusion injury to the lower limb leads to systemic endotoxaemia[19]. It has been suggested that the gut is the most likely source of endotoxaemia. An increase in intestinal permeability has been reported following abdominal aortic aneurysm surgery, a procedure that may lead to colonic ischaemia consequent upon ligation of the inferior mesenteric artery[13,14,20]. However the findings in this study indicate that isolated ischaemia–reperfusion injury to the lower limb *per se* can lead to systemic endotoxaemia. The mechanism involved in the development of endotoxaemia is not entirely clear. An increase in intestinal permeability to macromolecules has been observed following ischaemia–reperfusion injury to the hind limb[21]. Similar alteration in intestinal permeability has been reported following other forms of trauma and has been attributed to generalized permeability damage termed 'whole body inflammation'[22–25].

Endotoxin is the lipopolysaccharide component of the cell membrane of Gram-negative bacteria. It has a wide range of toxic biological actions and is a recognized potent activator of various cellular and humoral pathways including the complement and coagulation cascades[26,27]

Table 1 Effect of ischaemia–reperfusion on plasma endotoxin concentration

	Control ($n = 12$)	3 h ischaemia ($n = 12$)	3 h ischaemia + 1 h reperfusion ($n = 12$)	3 h ischaemia + 2 h reperfusion ($n = 12$)	3 h ischaemia + 3 h reperfusio ($n = 12$)
Endotoxin (pg/ml)	2·5(0·9)	1·2(0·9)	10·0(3·0)*	44·8(19·2)*	20·2(6·2)*

Values are mean(s.e.m.). $*P < 0·05$ *versus* control (Mann–Whitney U test)

Table 2 Effect of ischaemia–reperfusion on plasma antiendotoxin antibody concentration

	Control ($n = 12$)	3 h ischaemia ($n = 12$)	3 h ischaemia + 1 h reperfusion ($n = 12$)	3 h ischaemia + 2 h reperfusion ($n = 12$)	3 h ischaemia + 3 h reperfusio ($n = 12$)
IgG (% of control value)	100 (11·2)	77·9 (9·9)*	71·1 (3·6)*	67·1 (3·1)†	68·4 (3·1)†
IgM (% of control value)	100 (8·1)	80·5 (9·7)*	70·1 (8·9)†	75·8 (8·9)*	79 (8·9)

Values are mean(s.e.m.). Ig, immunoglobulin. $*P < 0·05$, $†P < 0·005$ *versus* control (Mann–Whitney U test)

By activating macrophages and polymorphonuclear neutrophils endotoxin induces the production of an array of inflammatory mediators including different cytokines[28,29]. Together with these mediators, endotoxin causes metabolic derangement, vascular endothelial damage and cardiovascular changes that may result in hypotension and shock[30,31].

Although bacterial translocation has been demonstrated in a variety of other settings, it has not been observed following reperfusion of the ischaemic extremities despite the presence of endotoxaemia[9,32–36]. The clinical significance of bacterial translocation and whether it plays a role in the pathophysiology of MODS remains unclear. Deitch *et al.*[34] studied the relationship between endotoxin, intestinal mucosal injury and bacterial translocation. They concluded that the gut, under certain circumstances, may serve as an important port of entry for bacteria. Peitzman *et al.*[37] were unable to find any relationship between the development of sepsis and MODS and positive mesenteric lymph node culture in critically ill trauma patients. Other workers have shown that the occurrence of endotoxaemia is a more sensitive predictor of the development of sepsis syndrome than bacteraemia[38,39]. This may be due to the fact that translocated bacteria are killed in the mesenteric lymph nodes while endotoxin is released and disseminated[40]. Furthermore, endotoxin has been shown to permeate through the bowel more easily than intact Gram-negative bacteria[38]. This indicates that the detection of endotoxin may be clinically more significant than bacteraemia. This concept is supported by several clinical studies which have shown that, although selective gut decontamination causes dramatic reduction in colonization and effectively prevents bacterial translocation from the gut, it does not significantly reduce the mortality rate or hospital stay in critically ill patients[41]. In a study of patients with septic shock, endotoxaemia occurred in 43 per cent of patients but only 26 per cent of patients with endotoxaemia had Gram-negative bacteraemia[42]. Similar findings were reported in other studies[43,44].

Antibodies produced by the host against the inner core glycolipid (EndoCAb) offer some protection against different strains of bacteria and the toxic effects of the lipopolysaccharide[45]. The decrease in endogenous antibodies (EndoCAb) observed in animals following lower limb ischaemia–reperfusion provides further evidence in support of the development of endotoxaemia. Antiendotoxin antibodies are consumed by the formation of endotoxin–antibody complexes thus neutralizing endotoxin and lowering its plasma concentration. The depletion of these endogenous EndoCAb antibodies has been found to be associated with significantly higher endotoxin levels in patients with sepsis. Moreover, patients with a low IgG EndoCAb level on admission had a significantly higher mortality rate[44]. This implied that endogenous EndoCAb concentration may be of value in predicting outcome in patients with sepsis syndrome. The fact that 74 per cent of patients had normal circulating levels of these antibodies suggests that the low level of antibody is a reflection of the degree of endotoxaemia rather than a cause of it.

It is worth noting that a reduction in antiendotoxin antibodies was also observed in animals that were ischaemic but not reperfused although there was no accompanying increase in endotoxin in these animals. A possible explanation is that some degree of reperfusion and endotoxaemia occurred in these animals before tourniquet release owing to incomplete ischaemia of the limbs. A significant decrease in endogenous EndoCAb has been reported following major surgery and it is conceivable that the decrease in antiendotoxin antibodies was part of a generalized decrease in immunoglobulin levels and not specific for endotoxin[11]. To elucidate this further, experiments should be carried out in animals immunized against tetanus toxoid, with measurement of antitetanus toxoid antibodies, in addition to antiendotoxin antibodies, as a marker of the generalized decrease in plasma immunoglobulins.

In conclusion, this study shows that endotoxaemia may occur following reperfusion of ischaemic hind limbs. Bacterial translocation does not seem to be a prerequisite for endotoxaemia. Studies of the systemic inflammatory response and end-organ function are currently under way to determine whether endotoxaemia contributes to the systemic complications observed following lower limb ischaemia–reperfusion in patients undergoing abdominal aortic aneurysm surgery.

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Prospective randomized controlled trial to compare skin staples and polypropylene for securing the mesh in inguinal hernia repair

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Background The Lichtenstein tension-free repair has become the standard method for repairing inguinal hernia in many surgical units. This study compared two methods of mesh fixation.

Methods Fifty men undergoing unilateral primary Lichtenstein inguinal hernia repair under general anaesthesia were randomized into two groups. In the control group polypropylene mesh was secured with 2/0 polypropylene sutures and the skin closed with subcuticular 3/0 polydioxanone. In the study group polypropylene mesh was secured with skin staples and the skin was closed with staples from the same staple gun. Duration of the operation was recorded. Early follow-up was achieved by patient review at 6 weeks and postal questionnaire at 12 weeks.

Results The operation was significantly shorter when staples were used (median 20 min 0 s *versus* 29 min 30 s, $P < 0{\cdot}001$). There was no significant difference in the incidence of postoperative complications or pain score. The study group reported earlier return to normal activity (4 weeks 0 days *versus* 6 weeks 2 days, $P < 0{\cdot}01$) although there was no difference in the time taken to return to work or driving.

Conclusion The use of skin staples to secure mesh in the Lichtenstein inguinal hernia repair significantly reduced the duration of the operation and was as effective as conventional mesh fixation with polypropylene in the short term.

The Lichtenstein repair is a tension-free inguinal hernia repair in which a sheet of polypropylene mesh is used to strengthen the transversalis fascia[1]. The standard way of securing the mesh in position on the posterior wall of the inguinal canal is with polypropylene sutures. A technique has been described in which skin staples are used for anchoring the mesh in position and early results have been favourable[2]. Concerns have been expressed, however, that the use of staples may lead to entrapment neuropathy[3,4], increased rate of wound infection[4], potential vascular injury[3,5,6] and increased cost[3]. This modification of the Lichtenstein technique was investigated in a randomized, prospective controlled trial to address these concerns and establish whether the use of staples leads to an effective repair.

Patients and methods

Fifty patients having elective repair of a unilateral primary inguinal hernia were entered into the trial. Informed consent was obtained. Patients were randomized either to the control group (where mesh was secured with polypropylene sutures) or the study group (where the mesh was secured with staples) in the operating room by sealed envelope.

All operations were performed under general anaesthesia by a consultant surgeon (D.A.R.). An ilioinguinal nerve block was inserted with bupivacaine 0·5 per cent by the anaesthetist and a single dose of intravenous co-amoxiclav 1·2 g was administered immediately before the operation began.

Direct hernia sacs were plicated unless very small, when they were reduced unopened. Indirect sacs were dissected from the spermatic cord and then divided, transfixed and excised. A sheet of polypropylene mesh (11 × 6 cm) was cut to shape and laid over the posterior wall of the inguinal canal so that it overlapped the pubic tubercle by at least 1 cm medially, extended superiorly to lay over the conjoint tendon and to a point at least 2 cm lateral to the internal ring. In the control groups this was fixed in position by a continuous suture of 2/0 polypropylene along the inguinal ligament inferiorly from the pubic tubercle to the lateral edge of the mesh. Interrupted polypropylene sutures were then placed medially and superiorly into the internal oblique and transversalis muscles. The spermatic cord was passed through the slit in the mesh. Lateral to it the overlapping free edges of the mesh were sutured together with two interrupted polypropylene sutures. In the study group the positioning of the mesh was identical but a Proximate RH Rotating Head Skin Stapler (Ethicon, Edinburgh, UK), containing 35 preloaded stainless steel staples, was used to secure it. A staple was placed into the pubic tubercle with between seven and nine staples along the inguinal ligament placed 1–2 cm apart. A further eight to ten staples were placed in the internal oblique and transversalis muscles medially and superiorly and the overlapping free edges of the mesh were stapled together with two staples lateral to the cord. In both groups the external oblique aponeurosis was closed with a continuous suture of 2/0 Vicryl (Ethicon, Edinburgh UK) and the subcutaneous tissues were then approximated with the same suture. Skin closure was completed in the control group using a continuous suture of subcuticular 3/0 polydioxanone which was subsequently left in place. In the study group skin closure was completed using staples from the same staple gun and these were removed 7 days after operation.

The time taken from the first incision to the beginning of the hernia repair (defined as start of preparation of the mesh) and from the beginning of the mesh insertion to completion of skin closure were recorded to the nearest 5 s.

Patients were provided with a supply of oral coproxamol after operation and were discharged home when considered safe. Some patients were kept in hospital overnight for social, as opposed to surgical, reasons.

All patients were reviewed in an outpatient clinic 6 weeks after operation. Some 12 weeks after operation they were asked to complete a standard questionnaire and return by post. This requested information concerning complications of surgery, general practitioner (GP) call out or visit following discharge and time taken to return to work, normal activities and driving. Patients were also asked on the questionnaire to assess how much pain they had suffered after the operation on a 100-mm visual analogue scale. Patients who did not return the question-

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naire within 4 weeks were contacted by telephone and reminded to complete and return it.

Statistical analysis was performed using the χ^2 test with Yates' correction, Fisher's exact probability test and the Mann–Whitney *U* test.

Results

Patients

There were 25 patients in each group. The distribution of age, side of hernia and type of hernia was well matched between groups (*Table 1*). Forty-eight patients attended for outpatient review at 6 weeks and 46 patients completed the questionnaire.

Duration of surgery

The median duration of operation in the study group was 20 min 0 s compared with 29 min 30 s in the control group ($P < 0{\cdot}001$; *Table 2*). This difference was accounted for by the difference in time from the beginning of the mesh insertion to the end of operation.

Length of postoperative hospital stay

Seven patients in each group were treated as day cases, while 13 patients in the study group and 11 patients in the control group were discharged on the first postoperative day. Two patients in the control group had to be kept in hospital for more than 2 nights after operation: one for 5 days because of pain and poor social support and one for 7 days because of the development of a large scrotal haematoma.

Table 1 Clinical details

	Staples	Polypropylene
Median (range) age (years)	57·5 (21–82)	61 (18–75)
Type of hernia		
Right : left	13 : 12	16 : 9
Direct : indirect	7 : 18	8 : 17

Complications

Three patients in the study group and six in the control group suffered a minor complication. Four patients developed a wound haematoma (two in each group) but none required reoperation and all settled spontaneously. The two superficial wound infections and cellulitis of the hand, at the site of an intravenous cannula, resolved following a short course of oral antibiotics (all in the control group). There were no cases of mesh infection. One patient in the study group who developed urinary retention after operation had a urethral catheter inserted by his GP and subsequently had a successful trial without catheter at home. One patient in the control group has persistent groin pain and remains under review with a possible diagnosis of nerve entrapment. There was no hernia recurrence during the short follow-up period in either group.

Postoperative pain

There was no difference in pain scores between the two groups (*Table 3*). Only one patient still had pain 12 weeks after operation (control group).

Postoperative rehabilitation

Ten of the 24 patients in the control group available for follow-up consulted their GP after operation compared with seven of 24 patients in the study group (*Table 3*). One of these in each group necessitated a GP's visit to the patient's home while the remaining consultations took place in the GP's surgery. Two of the patients in the study group visited their GP for removal of the staples alone while all the other patients in this group had staples

Table 2 Duration of hernia repair

	Staples time (min + s)	Polypropylene time (min + s)	*P*
Start to beginning of mesh insertion	13·40 (9·00–25·30)	12·30 (7·50–19·45)	>0·1
Beginning of mesh insertion to end	7·20 (5·40–11·25)	17·45 (10·05–25·45)	<0·001
Total operation time	20·00 (16·00–33·15)	29·30 (24·00–43·45)	<0·001

Values are median (range)

Table 3 Postoperative course

	Staples	Polypropylene	*P*
Pain score*	32 (0–84) (*n* = 23)	47·5 (0–100) (*n* = 20)	>0·1
No. of GP consultations	7 of 24	10 of 24	>0·2
Reason			
Complication	2	3	
Pain	0	3	
Removal clips	2	0	
Off-work certificate	1	2	
Check-up	2	2	
Return to normal activity*†	4 (0·6–12) (*n* = 23)	6·2 (0·5–14) (*n* = 22)	<0·01
Return to work*†	5·4 (1–13) (*n* = 14)	6 (0·4–12) (*n* = 11)	>0·1
Return to driving*†	3 (1–8) (*n* = 17)	3·5 (0·4–8) (*n* = 16)	>0·1

*Values are median (range); †weeks and days removed by the district nurse. This group reported earlier return to normal activity (4 weeks 0 days *versus* 6 weeks 2 days, $P < 0{\cdot}01$). There was, however, no significant difference in the time taken to return to work or driving.

Discussion

The Lichtenstein tension-free inguinal hernia repair is becoming increasingly popular in the UK because it offers an effective repair that overcomes many of the problems and criticisms associated with other techniques. It is relatively easier to learn and less technically demanding than the Shouldice repair which has until recently been the gold standard recommended by the Royal College of Surgeons of England[7]. A different way of securing the polypropylene mesh using staples has been described by Egger *et al.*[2], but has been met with some scepticism[3-6].

In the study group the staples which were left in the staple gun following mesh fixation were used to close the skin, for economic reasons. In the control group the skin was closed with a continuous subcuticular suture of polydioxanone which was previously the preferred method of skin closure. Although employment of different methods of skin closure removed the potential for a blinded study, it allowed comparison with a 'best practice' control group. All operations were performed by one consultant surgeon removing any bias that might have been attributed to grade or ability of the surgeon.

The median length of the operation was almost 10 min shorter when staples were used. This operating time compares favourably with previous reports for the Lichtenstein repair[8,9], and may be important because shorter operations may be associated with a reduced risk of wound infection and because this keeps the risk of general anaesthesia to a minimum.

The use of skin staples for securing the mesh was not associated with an increase in perioperative complications. The staples are made from stainless steel with an inert coating. The length of the prongs on the staples is 3·9 mm which appears sufficient to provide good penetration into the tissues, including the pubic tubercle, with secure fixation of the mesh. Risk of damage to major underlying vessels may be less than with insertion of conventional sutures. Accurate staple placement is facilitated by the design of the stapler, whose head rotates 360°, thereby allowing maximum visibility and improved access.

Patients in the study group reported that they returned to normal activity earlier than those in the control group. There was also a trend for patients in the study group to return to work and driving earlier, to consult their GP less and to report lower pain scores on a visual analogue scale, although none of these differences was statistically significant. This apparent earlier rehabilitation may be because patients in the study group saw the district nurse for removal of staples and thus potentially benefited from constructive and encouraging advice regarding rehabilitation. Overall, the patients' return to normal activity, work and driving in this study took longer than expected. The patients were seen and counselled before surgery by a consultant surgeon and were advised that it was likely that they should be able to return to driving after 7–10 days and normal activity and work after 2–3 weeks[10]. One explanation may be that these estimates were overcautiously interpreted by patients and their GPs[11].

This study has demonstrated that the technique of mesh fixation with skin staples in the Lichtenstein inguinal hernia repair is as effective as conventional fixation with polypropylene sutures in the short term. It also has an important advantage in significantly reducing operating time. Although the cost of consumables per operation is increased when staples are used, this cost should be carefully weighed against the more efficient use of operating time.

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Lichtenstein inguinal hernia repair in a primary healthcare setting

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Background Given the generally accepted poor outcome of inguinal hernia repair when using nylon darn, and the recent interest in low-tension mesh repair, an attempt was made to demonstrate the feasibility, outcome and patient perception of providing Lichtenstein inguinal hernia repair, using local anaesthesia, wholly within the primary healthcare sector.

Methods A prospective study reviewed clinical outcome and patient perception in 100 adults referred with inguinal hernia only. No selection was made regarding age, sex, American Society of Anesthesiologists status or previous repairs. Recurrence, pain, infection, return to full function and associated complications were assessed at 24 h, 1 and 6 weeks, and 1 year. Local Community Health Councils assessed patient perception.

Results In the first 100 patients (age range 21–83 (mean(s.d.) 60(14·7)) years; 58 of employable age; 92 men; ten recurrent hernias), no recurrences have occurred at 1 year. Infection rate was 3 per cent. Pain was maximal in the first 24–48 h (median visual analogue scale 5, range 0–10) and reduced rapidly (median 1) at 1 week. Mean time to return to work or full normal activity was 8 days. Some 85 operations were performed within 1 month of diagnosis. In all, 86 patients returned the patient satisfaction questionnaire and 98 per cent of these were 'very pleased' with the service.

Conclusion In highly motivated primary healthcare centres, inguinal hernia repair can be undertaken effectively, providing high patient satisfaction, minimal complications and low recurrence rates using the Lichtenstein technique.

In the early 1990s, the UK Department of Health commissioned a Royal College of Surgeons' working party to review hernia repair nationally. This identified groin hernia as 'one of a number of surgical interventions that accounted for the majority of long wait cases on waiting lists, for which there was a wide range of clinical practice and considerable variation in outcome'. It further concluded that, whilst fewer than 8 per cent of National Health Service (NHS) hernia repairs are performed as day cases, up to 30 per cent of elective hernioplasties could be so performed. In addition, the report emphasized that day surgery is cost effective, and that the establishment of recognized specialist centres could improve overall outcome[1].

Hernia repair has, until now, been the domain of the hospital sector, where traditional darn techniques have been associated with recurrence rates of up to 15 per cent, a hospital stay of a few days, significant postoperative pain and the prospect of return to normal function delayed for 6 weeks. General anaesthesia, with its own complications, is still used invariably in most NHS hospitals[1].

The Audit Commission of 1990 confirmed the economic benefits of day surgery[2]. More recent reports have shown the overall benefits to the patient of both mesh repair and the use of local anaesthesia[3]; however, to date, the role of the primary healthcare sector in providing daycare facilities has not been investigated.

The Lichtenstein Institute has published many reports outlining the use of polypropylene mesh in the repair of groin hernia[4–8]. Its conclusions were that, in conjunction with the 'tension-free' hernia repair, polypropylene mesh has the property of reinforcing abdominal wall hernias without significant risk of rejection, infection or seroma formation, by incorporation into body tissue by rapid fibrinous fixation[5]. A recurrence rate of 0·13 per cent at 5 years was reported using the Lichtenstein technique under local anaesthesia[6]. The technique allows for immediate postoperative ambulation, is well tolerated by the majority of patients, permits an early return to gainful employment (between 2 and 10 days)[7] and, in the present authors' opinion, is best suited to a dedicated primary healthcare setting.

The formal Lichtenstein repair was adopted by the authors, using local anaesthesia and polypropylene mesh (Marlex; Bard UK, Crawley, UK), and experience with this technique in the primary healthcare sector is reported.

Patients and methods

Study location

The health centre operates wholly within the NHS as a primary healthcare–general practice facility. It has a fully equipped operating suite, dedicated nursing personnel, and consulting and postoperative recovery rooms. From June 1994, an unpublished feasibility study of hernia repair with local anaesthetic was undertaken with visiting surgeons from the British Hernia Centre in London. Forty unilateral repairs were completed without complication. A prospective study was subsequently proposed using the services of a full-time surgically qualified partner of the practice (P.M.L.). Training and accreditation were gained by visits to the Lichtenstein Institute in Los Angeles and the London Hernia Clinic.

Protocol

The service was offered to all local NHS general practitioners, who would normally refer patients to established hospitals. At first appointment the need was assessed and the operation explained in full by the surgeon. Only patients with fully

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reducible hernias were accepted for the study. Verbal and written instructions were given, together with an opportunity to view a video recording explaining the procedure. Informed consent, blood and urine specimens were obtained and a date for operation was given. A named 24-h carer (usually a family member) was recorded and a relationship was established on a first-name basis. The groin area was shaved 24 h before operation and the patient was asked to starve from food for at least 4 h, and from fluids for 1 h, before operation.

On the day of operation, the patient was met by the receptionist, surgeon and scrub-nurse assistant. A full-time consultant anaesthetist was employed on an 'outreach' clinic basis on the day of operation to assess the patient, obtain intravenous access and continue full monitoring with pulse oximeter, electrocardiography, blood pressure and pulse readings throughout the procedure. Full resuscitation equipment and trained staff were available at all times. Immediate access to a surgical bed in a local acute hospital was available, should the need arise, as part of the study protocol.

Before operation suppositories of diclofenac 100 mg (Ciba, Horsham, UK) and prochlorperazine 25 mg (Rhone-Poulenc Rorer, Eastbourne, UK) were given, the incision was marked and the patient was taken to the operating table. Intravenous midazolam (Roche, Welwyn Garden City, UK) and fentanyl (Janssen-Cilag, High Wycombe, UK) were administered to procure light sedation. Continuous oxygen was given via nasal cannulas and the patient was further relaxed by listening to music through a head-set. Local anaesthesia was achieved following the protocol described by Amid and colleagues[8], and the operation was performed following the Lichtenstein protocol[6]. Digital examination of the femoral canal was made in all cases to exclude the presence of femoral hernia, which, if found, was repaired.

Postoperative observations continued for 3 h until the patient was able to eat and drink freely, walk painlessly and unaided, and had passed urine. Visual analogue scale pain assessments were recorded at 1 and 2 h by nurse and patient independently[9]. Patients were asked to make a mark, appropriate to the pain, on a linear 10-cm scale where 0 represents no pain and 10 is agony.

Postoperative management

Patients were advised to rest for a period of 24 h after which graduated exercise commenced. Warm baths were encouraged to ease wound discomfort and help soak off the covering dressing. Discharge medication included one 100-mg diclofenac suppository to be taken on the first night if required. Pain relief was otherwise provided as Co-dydramol (Sanofi Winthrop, Guildford, UK) and Ibuprofen (Brufen 400 mg; Knoll, Nottingham, UK) (one or two tablets, 4–6 hourly) as required. Three 24-h contact mobile telephone numbers were given to the patient: those of the surgeon, scrub-nurse assistant and health centre. Comprehensive written instructions were given to the patient and to the named carer, who were contacted at 24 h by the surgeon or scrub-nurse assistant. During the first week, the patient was asked to record daily the number of tablets taken and visual analogue pain score. At 1 week, wound assessment and complications were recorded, the subcuticular suture was removed and the patient was given an anonymized questionnaire, devised by the Community Health Council (CHC) to assess patient satisfaction. The CHC is a recognized, official, patients' advocate group. The questionnaires were completed independently at the patient's home and returned directly to the CHC offices by stamped addressed envelope, where they were appraised by a medical epidemiologist. Patients were also seen at 6 weeks and at 1 year, when similar data were collected.

Results

The results of the first 100 consecutive inguinal hernia repairs performed from September 1995 to June 1996 are presented. Two additional patients were referred to local hospitals and were not included in the study, one with a history of reaction to local anaesthetic and one who was unable to give the name of an appointed 24-h carer. *Table 1* summarizes characteristics of the 100 patients. *Table 2* gives details of the operative and anaesthetic techniques. Two patients had orchidectomy as an additional planned procedure: one was a 43-year-old man who presented with a small undescended testis, palpable at the internal ring, in association with an indirect hernia sac; the other, aged 76 years, presented with a second recurrence and orchidectomy was considered expedient. A Jaboulay procedure was performed in one patient with a concurrent primary hydrocele. No femoral hernia was found in this study.

Table 1 Patient characteristics ($n = 100$)

Mean(s.d.) (range) age (years)	60(14·7) (21–83)
No. aged under 65 years	58
No. employed	43
No. of manual workers	24
Sex ratio (M:F)	92:8
Waiting time from consultation to repair	
< 1 month	85
< 2 weeks	65
Hernia type	
Primary unilateral inguinal	90
Secondary or multiple recurrence	10

Table 2 Operative and anaesthetic detail ($n = 100$)

Volume of local anaesthetic agent used (ml)*	43 (28–60)
Amount of intravenous sedative used*	
Midazolam (mg)	4·8 (2–10)
Fentanyl (μg)	65 (40–100)
Operating time (min)	40 (25–61)
Hernia type	
Indirect unilateral	68
Inguinoscrotal	13
Direct unilateral	13
Mixed	19
Type of repair	
Full mesh	95
Mesh plugs	5
Additional procedures	
Orchidectomy	2
Jaboulay procedure	1

*Values are mean (range)

In the postoperative observation period, only three patients recorded a score of 1 (minimal pain) on the visual analogue pain scale at either 1 or 2 h. All other patients recorded zero pain on the scale. One patient experienced paraesthesia in an L1–3 distribution, representing a partial femoral nerve block, for a period of 6 h; there were no lasting effects. All patients left the department at 3 h, pain free, fully mobile and satisfied with the procedure. The facility of immediate access to a hospital surgical bed was not used. At 24 h all patients were contacted; only two home visits were undertaken, by the surgeon who offered advice only. All patients returned for appointments at 1 and 6 weeks; 85 have attended the yearly assessment so far. *Fig. 1* shows the median and interquartile range pain scores recorded by patients using the 10-cm 0–10 visual analogue scale for up to 6 weeks. Postoperative nausea and vomiting did not occur, and there were no recorded instances of cardiovascular, respiratory, circulatory or obstructive urinary complications. Other complications are shown in *Table 3*. No complications were recorded at 1 year (85 patients).

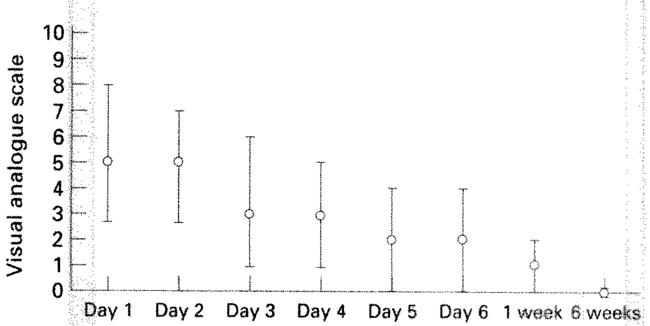

Fig. 1 Median and interquartile range of pain scores

Table 3 Complications recorded at follow-up appointments ($n = 100$)

Complication	1 week	6 weeks
Sepsis		
Superficial (<2 cm)	2	3
Deep (suppurative)	1	0
Swelling		
Minimal (<2 cm)	11	0
Moderate (>2 cm)	10	2
Severe or scrotal	3	0
Bruising		
Minimal (<2 cm)	31	0
Moderate (>2 cm)	10	2
Severe or scrotal	1	0
Abnormal testes	0	0
Recurrence	0	0

Table 4 Patient perception of peroperative care

Question	Percentage of patients*
Were you given written information about what to expect at your operation?	98
Was the procedure explained to you?	100
Did you fully understand that explanation?	98
Did you sign a consent form?	94
Was each stage of your operation explained to you?	86
Were you comfortable during the operation?	100
Did you feel any pain during your operation?	0
What was the room temperature during your operation?	
Hot	0
Cold	0
Comfortable	85
Did not notice	15
Did you feel embarrassed during your operation?	0
Were you given enough privacy during your operation?	100
During your operation, were you attended by a nurse?	98
At any stage during the operation did you	
Ask them to stop?	0
Ask for more pain killers?	0
Talk freely to the nurse/doctor?	100
Were you given a contact number for questions/problems?	98
Were you told how to look after your wound?	98
Were you advised on pain relief?	98
Did you have a follow-up appointment?	100
Would you have another operation in the health centre if you needed one?	100
Would you recommend this service to your friends?	100
Were you pleased with the service and care you received?	98

*Values are the percentage of 'Yes' responses to the nearest whole number ($n = 86$)

Table 5 Patient perception of postoperative recovery

	Immediate	First 24 h	First week
Did you have any pain?			
Yes, a lot	2	22	6
Yes, some	4	40	16
Yes, a little	10	18	36
Not really	16	2	8
No, not at all	38	8	8
No response	30	10	26
Did you have any problem with your wound?			
No	98	98	98
No response	2	2	2

Values are percentages to the nearest whole number

Patient perception survey

The results of this survey have been published in detail elsewhere[10]. Eighty-six patients returned the patient perception questionnaire (*Tables 4* and *5*). Of these, 67 (78 per cent) offered individualized written comments; 84 patients (98 per cent) were 'very satisfied' with the service overall. Mean(s.d.) time to return to work, or normal function, as perceived by the patients, was 8(6·1) (range 1–25) days.

Discussion

It is generally agreed that all indirect and symptomatic groin hernias should be repaired[1]. In the UK inguinal hernia represents 6 per cent of all surgical admissions, 8 per cent of all general surgical operations and occupies 5 per cent of all general surgical beds. Furthermore, 18 per cent of general surgical waiting lists comprise elective hernia repair[1]. In total, more than 80 000 hernias are repaired annually in the UK[1]. Given that these figures are based on primary referral figures, the true prevalence of hernia disease is almost certainly higher, a fact supported by 40 000 trusses being prescribed annually[11]. Recurrence rates of over 10 per cent outside dedicated centres have been suggested, perhaps reflecting non-standardization of operative technique[12].

The Lichtenstein Institute in Los Angeles, the Shouldice clinic in Toronto and the London Hernia Clinic have introduced the prospect of day-case hernia repair associated with little postoperative pain, recurrence rates of less than 1 per cent and a return to normal function within days. Day-case and short-stay hernia repair in hospital facilities have become more widespread[3] in the 1990s, but the authors are not aware of any report of day-case hernia repair carried out in the primary healthcare sector.

This study has indicated that the present-day 'gold standards' can be reproduced safely and effectively in a dedicated, and highly motivated, primary healthcare centre. Such centres could ease the workload of acute general hospitals in the future and provide a programme of postgraduate teaching for surgeons and anaesthetists in training, thereby ensuring a reproducible standard of both care and outcome.

An attempt was made to compare patient satisfaction in the present patients and those operated on at an existing day-case facility in a local acute hospital, using the same CHC questionnaires. However, the low return rate of questionnaires from patients using the acute hospital ($n = 13$) rendered comparison futile.

While it is clear that not all general or family practices have the expertise or facilities to establish such centres, it may be anticipated that, in keeping with the current political emphasis on shift from secondary to primary care, coupled with the probable cost savings, similar specialist primary healthcare units will develop outreach clinics from local acute hospitals.

Acknowledgements

Special thanks go to Dr Julie Smith, Chief Officer, Basildon and Thurrock Community Health Council, Beryl Furr, Chief Officer, Southend Community Health Council, Dr Alex Shulman (recently deceased) of the Lichtenstein Institute and Mr M. Notoras of the London Hernia Clinic.

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Randomized placebo-controlled trial of local anaesthetic infusion in day-case inguinal hernia repair

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Background This study investigated the efficacy of local anaesthetic wound perfusion following day-case inguinal hernia repair.

Methods Seventy-two patients entered a randomized controlled trial with three patient groups: group 1, pump containing bupivacaine; group 2, pump containing normal saline; and group 3, control group without a pump. All patients had a Lichtenstein hernia repair together with ilioinguinal and iliohypogastric nerve blocks and were prescribed oral analgesia. Postoperative pain was assessed over 5 days using a visual analogue scale.

Results Patients who had a local anaesthetic infusion had significantly less pain than either the placebo or control groups. This was greatest during the first 48 h (day 1, $P = 0{\cdot}028$ and 0·011 respectively; day 2, $P = 0{\cdot}012$ and 0·037 respectively).

Conclusion A portable infusion pump for the delivery of local anaesthetic reduced pain after day-case inguinal hernia repair.

Day surgery is increasing in the UK; it is predicted that it will account for up to 50 per cent of all surgical procedures performed in the next decade[1,2]. Postoperative pain is a major factor which reduces its acceptability to patients[3]. After day-case inguinal hernia repair 10 per cent of patients have severe postoperative pain requiring the services of a general practitioner (GP) to administer intramuscular opiates[4]. This can be reduced by the use of oral opiates, and pre-emptive and postoperative blockade with locoregional anaesthesia[5–8]. Oral opiates may cause nausea unacceptable to some patients[9]. Locoregional anaesthesia is effective[5,7,8] but is limited in duration of action, even when using long-acting agents such as bupivacaine[7]. Continuous infusion of local anaesthetic into a surgical wound can reduce postoperative opiate requirements[10–12]. Until recently there was not a delivery system suitable for use in day-case surgery.

The authors investigated the use of an infusion pump for the delivery of local anaesthetic for day-case hernia repair.

Patients and methods

Seventy-two consecutive patients undergoing standard unilateral inguinal hernia repair as a day case were included in the trial. Informed consent, as approved by the local ethics committee, was obtained in each case. Each patient was randomized to one of three groups: group 1, pump containing bupivacaine; group 2, pump containing normal saline; and group 3, control group without a pump. Group 3 was included to demonstrate the size of the placebo effect and to exclude the possibility of a negative effect of the placebo.

A Lichtenstein hernia repair[13] was used in every case. Standard sutures were 2/0 polypropylene to sew in the polypropylene mesh, 1/0 polyglactin to close the external oblique aponeurosis and 3/0 subcuticular polydioxanone for skin. Surgery was carried out under general anaesthesia with additional ilioinguinal and iliohypogastric nerve blocks performed before the skin incision using 0·5 per cent bupivacaine 10 ml in every patient. The wound catheter (16-G epidural catheter) was inserted under direct vision under the external oblique aponeurosis before closure and brought out through a separate stab wound laterally. At the end of the procedure the wound was dressed and the pump connected to the wound catheter.

The pump, a Baxter Daymate Elastermeric infusion device (Baxter Healthcare, Thetford, UK) (*Fig. 1*), delivered 2 ml/h and was filled with 100 ml of either normal saline or 0·5 per cent bupivacaine in accordance with a randomization envelope, hence providing an infusion for 50 h. The surgeons, patient and liaison nurse visiting the patient at home remained blinded to the randomization until the end of the trial.

All patients were prescribed oral analgesia with Aspav (Hoechst Marion Roussel, Uxbridge, UK) which they were instructed to take every 4–6 h, to a maximum of eight tablets every 24 h. If necessary, opiates were given in the recovery area or by the GP and their use was recorded.

A liaison nurse visited the patient at home, approximately 48 h after the operation (routine practice) and, as well as her usual checks, removed the pump and wound catheter.

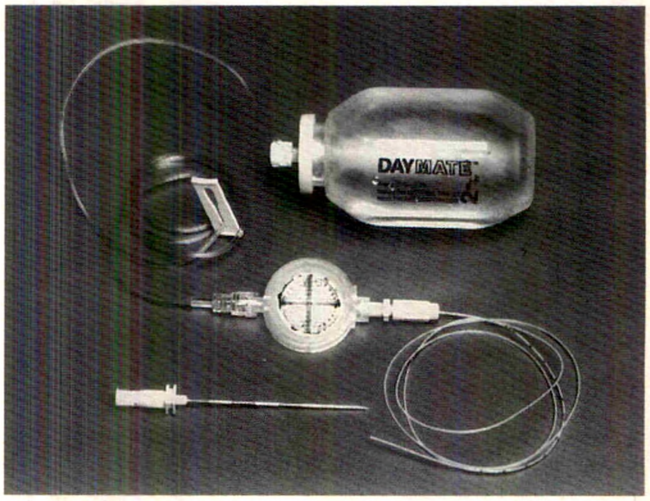

Fig. 1 Baxter device primed with local anaesthetic and attached to the wound catheter. Also shows the trocar used to bring the catheter out through the skin and the bacterial filter

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Patients were asked to complete a questionnaire recording the pain they had felt over the previous 24 h for each of the 5 days following operation. This was recorded on a visual analogue scale (VAS). Patients were also asked to record additional analgesics used including any injections given by an emergency doctor.

All patients were reviewed in the outpatient department 4 weeks after surgery and the wounds inspected.

Analysis of the results was made with the Mann–Whitney *U* test using Minitab for Windows (Microsoft) version 10.2. $P<0{\cdot}05$ was considered significant.

Results

The patient groups were comparable in age and sex (*Table 1*).

Infusion of bupivacaine for 50 h after operation significantly reduced the VAS score recorded by patients when compared with placebo and control groups (day 1, $P=0{\cdot}028$ and 0·011 respectively; day 2, $P=0{\cdot}012$ and 0·037 respectively) (*Fig. 2*). Over the remaining 3 days recorded pain differences between the groups slowly equilibrated. There was no rebound increase in pain at the end of the bupivacaine infusion.

There was no significant difference in the analgesic requirement between the groups (*Table 2*). Four patients developed a wound infection (one in group 1, one in group 2 and two in group 3). No patient developed nerve entrapment or significant hypoaesthesia and all wounds were well healed at the 4-week review.

Table 1 Age and sex distribution

Group	No. of patients	Mean (range) (years)	Sex ratio (M : F)
1	25	53 (17–83)	23 : 2
2	24	58 (21–78)	22 : 2
3	23	56 (23–81)	23 : 0

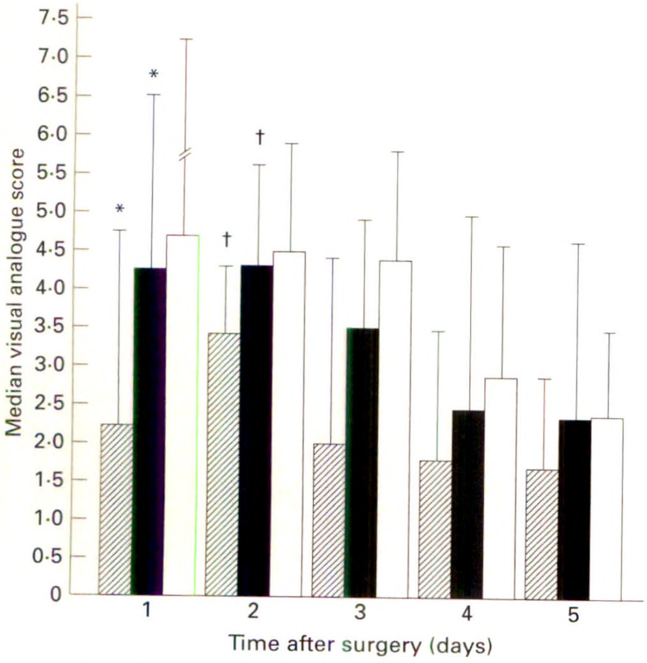

Fig. 2 Daily median pain scores reported by patients in each study group as measured with the visual analogue scale. ▨, Pump containing bupivacaine; ■, pump containing normal saline; □, no pump. Scores are presented as median with 75th percentile (bars). $^{*}P=0{\cdot}028$; $^{\dagger}P=0{\cdot}012$ (Mann–Whitney *U* test)

Table 2 Analgesic use

Group	Median no. of Aspav tablets per day	No. of patients requiring intramuscular analgesia
1	3·0	1
2	3·5	2
3	4·0	3

Discussion

The Baxter Daymate Elastomeric Infusion Device is a portable, disposable, low-cost perfusion pump that delivers fluid reliably at a fixed rate. The pump provides postoperative analgesia safely and at a level equivalent to that of oral opiates without the associated nausea[9]. In the present study the infusion of bupivacaine for 50 h after operation resulted in significantly less pain than in either the placebo or the control group as measured with a standardized 10-cm VAS. This effect seemed to be prolonged after the end of the infusion possibly because of prevention of sensitization of the central nervous system. This effect may be potentiated by an increase in the duration of the neuronal blockade[14,15]. These results were obtained in patients having the hernia repair believed to produce the least postoperative pain[13] together with ilioinguinal and iliohypogastric nerve blocks[5,7]. The clinical advantage of this method for day-case surgery is the ability to provide adequate analgesia safely with regard to the peak plasma levels of bupivacaine[9,16]. There was no increase in the incidence of wound infection and no patient in the study had a deep wound infection.

The position of the catheter under the aponeurosis is a more effective site than subcutaneously[17]. No patient suffered an iatrogenic femoral nerve block. There was no significant difference in the additional analgesic use between the groups. Of the 72 patients in the study, six required additional parenteral analgesia, but only one after bupivacaine infusion.

The use of a pump for local anaesthetic wound perfusion after inguinal hernia repair is an effective method of reducing postoperative pain and is suitable for day surgery.

Acknowledgements

The authors thank Baxter Healthcare for supplying the Daymate pumps used in this trial.

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J ileal pouch–anal anastomosis for chronic ulcerative colitis: complications and long-term outcome in 1310 patients

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Aim The purpose of the study was to determine the risk of postoperative complications and the functional outcome after a hand-sewn ileal pouch–anal anastomosis (IPAA) for ulcerative colitis using a single J-shaped pouch design.

Methods Preoperative function, operative morbidity and long-term functional outcome were assessed prospectively in 1310 patients who underwent IPAA between 1981 and 1994 for ulcerative colitis.

Results Three patients died after operation. Postoperative pelvic sepsis rates decreased from 7 per cent in 1981–1985 to 3 per cent in 1991–1994 ($P = 0·02$). After mean follow-up of 6·5 (range 2–15) years, the mean number of stools was 5 per day and 1 per night. Frequent daytime and night-time incontinence occurred in 7 and 12 per cent of patients respectively, and did not change over a 10-year period. The cumulative probability of suffering at least one episode of 'clinical' pouchitis was 18 and 48 per cent at 1 and 10 years and the cumulative probability of pouch failure at 1 and 10 years was 2 and 9 per cent respectively.

Conclusion These results indicate that increased experience decreases the risk of pouch-related complications and that with time the functional results remain stable, but the failure rate increases.

Ileal pouch–anal anastomosis (IPAA) for chronic ulcerative colitis was first described in 1978[1], and has since become a well established procedure. However, it is a technically demanding operation which can be associated with serious complications, especially sepsis, which may have a detrimental effect on outcome[2,3]. It is thus important to know whether the incidence of major complications, noted in previous publications to affect up to 54 per cent of patients[4–17], decreases with increasing experience. Early bowel function following IPAA has been demonstrated to be acceptable[4–18], but it is uncertain whether function changes significantly over prolonged follow-up. Similarly, the incidence of long-term complications of IPAA, particularly pouchitis and small bowel obstruction during extended follow-up, is not known. Early pouch failure, with excision of the pouch or creation of a permanent ileostomy, is generally uncommon, although published rates have varied between 2 and 22 per cent[4–10,12–14,16–18]. The incidence and causes of late pouch failure remain to be determined. Finally, many reports on the IPAA include various configurations of reservoirs with or without 'mucosectomy' performed in patients afflicted by different diseases, all of which may influence outcome.

The objective of this study was to examine the long-term results of the J-shaped pouch for chronic ulcerative colitis only. Specific emphasis has been placed on the effect of increasing surgical experience on postoperative morbidity, the changes in bowel function with prolonged follow-up and the long-term incidence of pouchitis and late pouch failure.

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Patients and methods

Between January 1981 and December 1994, 1608 patients underwent IPAA in this centre, 1410 (87 per cent) of which were for chronic ulcerative colitis. Of these 1410 patients, 54 had coexisting cancer and were excluded from further analysis. The type of pouch constructed in the remaining 1356 patients was J shaped in 1310 (97 per cent), S shaped in 27 (2 per cent), W shaped in 17 (1 per cent) and lateral–lateral in two. Most patients had diverting ileostomies constructed at the original pouch procedure, but 56 (4 per cent) did not.

All patients were followed by a nurse research assistant who first collected preoperative data and then contacted the patients by telephone 6 months after ileostomy closure, and then yearly by written and/or telephone questionnaire. Surgeons did not contribute to data collection. Data accrued included details of preoperative bowel, urinary and sexual function, operative morbidity and mortality, postoperative stool frequency, continence data, the ability to distinguish gas from stool, medication requirements, episodes of pouchitis and pouch failure. For the purpose of IPAA follow-up, daytime and night-time faecal incontinence was characterized as nil, occasional spotting (two or fewer episodes per week and no interruption of daily activities), or frequent (more than two per week with interruption of daily activities) or gross faecal soiling. Pouchitis was identified clinically by the sudden onset of frequent, watery, sometimes bloody, stools with urgency, often associated with abdominal cramping, malaise and fever. An episode of pouchitis was considered to have occurred if a patient suffered the above symptoms for more than 2 days, and symptoms were relieved within 48 h by metronidazole or other antibiotics. Pouch failure indicated that the pouch was excised or a diverting ileostomy was required for more than 1 year.

The mean age of patients at IPAA was 33 (range 5–65) years. There were 689 male and 621 female patients. Before operation, mean stool frequency per day was 10 (range 1–35) and 7 per cent of patients had episodes of faecal incontinence; 14 per cent did not participate in any form of sexual activity and a further 73 per cent reported reduced sexual activity.

The operative technique of IPAA has been described previously[8]. A diverting ileostomy was performed in 96 per cent of patients. The ileostomy was closed a mean of 97 days after operation. Three hundred patients had completed follow-up at 1, 5 and 10 years after surgery.

Statistical analysis

Proportions of events were compared in two groups with the χ^2 or Fisher's exact test. Comparison of ordinal variables, such as daytime and night-time number of stools, were compared in two groups with the Wilcoxon rank sum test. Changes over time within an individual in ordinal variables were assessed with the Wilcoxon rank sum test. The association of ordinal variables with one another, or of ordinals with continuous variables, was assessed with Spearman's rank correlation coefficient. The cumulative probabilities of pouchitis, pouch failure and small bowel obstruction were estimated by means of the Kaplan–Meier survivorship method. Results are expressed as mean (range).

Results

Postoperative morbidity and mortality

Three patients died after operation. One patient died from a massive pulmonary embolism 2 weeks after discharge from hospital, another died several weeks after suffering complications of a perforated gastric ulcer, and one patient died from a subarachnoid haemorrhage.

The overall complication rate within the immediate postoperative period was 19 per cent. Pelvic sepsis occurred in 74 patients (6 per cent). Seventy-three of these patients experienced sepsis as a result of the pouch procedure whereas one did so because of a perforated gastric ulcer. Twenty-seven patients were treated by antibiotics alone ($n = 11$) or in combination with computed tomographic drainage ($n = 16$), while 46 patients (63 per cent) required operative intervention. Abdominal wound infection occurred in 39 patients (3 per cent). Some 195 patients (15 per cent) developed a perioperative episode of small bowel obstruction, with 47 requiring laparotomy.

Fifteen patients (1 per cent) never had the ileostomy closed. Six of these patients preferred to have the stoma for personal reasons. Of the remaining nine patients, reasons for failure to close the ileostomy were pelvic abscess ($n = 5$), poor anal squeeze effort ($n = 1$), peritonitis ($n = 1$), pouchitis ($n = 1$) and unknown reasons ($n = 1$).

With increasing experience the incidence of postoperative sepsis decreased significantly, from 7 per cent in 1981–1985 to 3 per cent in 1991–1994 ($P = 0\cdot02$). During the same time periods, wound infection rates were similar at 2 and 1 per cent respectively.

Stool frequency

At discharge from hospital the patients had a mean stool frequency of 6 (range 1–17) per day and 1 (range 0–9) per night. Seventy-nine per cent were always continent, 19 per cent had occasional incontinence and 2 per cent suffered frequent incontinence. Thirty per cent were discharged on Lomotil (Searle, Chicago, Illinois, USA), 19 per cent on loperamide and 4 per cent on a bulk-forming agent.

After a mean follow-up of 6·5 (range 2–15) years the mean number of stools per day was 5 (range 1–20) and the number of stools per night was 1 (0–15). The number of stools per 24 h was 6 (1–20), which was significantly less than before operation (10 (1–35) per 24 h) ($P < 0\cdot0001$).

Continence status

Fifty-four per cent of patients had normal continence during the day, 39 per cent had occasional mucous spotting and 7 per cent suffered frequent episodes of incontinence; 17 per cent wore a protective pad. Thirty per cent never leaked at night, 59 per cent had occasional mucous spotting and 12 per cent suffered frequent incontinence. There was no significant difference in these parameters between male and female patients, except that women were fully continent at night more often than men (45 *versus* 37 per cent).

Statistically, there was a significant correlation between preoperative stool frequency and stool frequency at last follow-up ($P = 0\cdot0001$). No significant correlation was noted between preoperative and postoperative incontinence ($P = 0\cdot84$).

To assess the change in bowel function with prolonged follow-up, the 300 patients who had follow-up at 1, 5 and 10 years were analysed separately. The number of stools remained the same at 1 and 10 years (mean daytime frequency 5·7; mean nocturnal frequency 1·2). Overall, bowel function was stable, with no significant change in continence from the 5-year follow-up to 10 years (*Tables 1* and *2*) Perineal skin irritation did not change in incidence with long-term follow-up for the entire group, and the need to take antidiarrhoeal medication decreased, but not significantly (*Table 3*).

Table 1 Incidence of daytime incontinence in 300 patients followed for 1, 5 and 10 years

Incontinence	1 year	5 years	10 years
None	80	76	73
Occasional	19	22	25
Frequent	1	2	2

Values are percentages

Table 2 Incidence of nocturnal incontinence in 300 patients followed for 1, 5 and 10 years

Incontinence	1 year	5 years	10 years
None	59	59	48
Occasional	49	38	44
Frequent	2	3	8*

Values are percentages. *$P < 0\cdot05$ *versus* 1 year (Wilcoxon rank sum test)

Table 3 Functional outcome in 300 patients at 1, 5 and 10 years

	1 year	5 years	10 years
Wears a pad	25	22	15
Takes antidiarrhoeal medication	48	37	39
Perineal irritation	56	44	51
Can distinguish gas from stool	70*	82	87
Sexual dysfunction	14*	7	8

Values are percentages. *$P < 0\cdot05$ (1 year *versus* 5 and 10 years, Wilcoxon rank sum test)

Sexual dysfunction

At last follow-up, ten men (1 per cent) reported impotence and 13 (2 per cent) reported retrograde/lack of ejaculation that was not present before operation. In addition, 21 women (3 per cent) reported dyspareunia and 18 (3 per cent) reported fear of leakage of stool during intercourse. It was apparent that the number of patients who reported sexual dysfunction after IPAA improved as compared to 1 year (*Table 3*).

Long-term small bowel obstruction

Following closure of the ileostomy 202 patients (15 per cent) developed at least one episode of small bowel obstruction. Of these, 93 (46 per cent) were treated conservatively. The cumulative probability of developing small bowel obstruction 5 years after ileostomy closure was 14 per cent, whereas at 10 years it was 22 per cent.

Pouchitis

In all, 559 patients suffered at least one episode of pouchitis. The cumulative risk of suffering at least one episode was 18 per cent at 1 year after IPAA and 48 per cent at 10 years. Some 394 of the 559 patients who had at least one attack of pouchitis suffered a second episode. The cumulative probability of suffering a second episode after an initial attack within 2 years of IPAA was 64 per cent. Age, sex and postoperative sepsis did not influence the risk of developing pouchitis.

Pouch failure

A total of 134 patients (10 per cent) were considered to have suffered pouch failure at last follow-up (84 pouch excisions and 50 defunctioning ileostomies). The overall pouch failure rate was dependent on the length of follow-up. The cumulative probability of pouch failure was 2, 5 and 9 per cent at 1, 5 and 10 years respectively after IPAA.

Three pouches were excised within 30 days of surgery for ischaemia. Chronic sepsis was the commonest cause of pouch failure within 2 years of surgery ($n = 40$) and generally presented as recurrent pelvic abscesses, with or without fistulas. The symptoms of poor functional outcome, the second most common cause of pouch failure ($n = 26$), were usually increased stool frequency with incontinence and perineal irritation. No pouch has been excised for poor function since 1989. Twenty-one patients (2 per cent) had rediversion after initial closure of the stoma. Poor function ($n = 6$), pelvic sepsis ($n = 6$), pouch fistula ($n = 4$), Crohn's disease ($n = 3$), anastomotic stricture ($n = 1$) and pouchitis ($n = 1$) were the principal reasons.

Discussion

This study indicates that 91 per cent of patients followed for 10 years had a functioning IPAA. Among these, mean stool frequency was 6 per 24 h, and about 90 per cent of patients had either no incontinence or rare spotting. Bowel function during this prolonged follow-up has been relatively stable. Postoperative morbidity has been acceptably low. It is evident from this study that the IPAA remains a viable and appropriate surgical procedure in the treatment of chronic ulcerative colitis.

The incidence of pelvic sepsis following IPAA in published series has varied widely, from 0 to 24 per cent[4–17], and it is likely that a number of factors, including operative technique, patient selection, the proportion of patients with familial adenomatous polyposis and the methods of diagnosing sepsis may explain these differences. More recent and larger series have noted pelvic sepsis in 5–14 per cent of patients[11,16,17]. The present study shows that with increasing experience significant decrease in pelvic sepsis occurs. Patients who require reoperation for pelvic sepsis are at increased risk of pouch excision[2,3]. While a temporary ileostomy does not protect the patient against sepsis and may be associated with significant morbidity[19], the authors still establish a temporary ileostomy in most patients in an attempt to decrease the incidence and consequences of pelvic sepsis. A number of authors[20–24] and a recent randomized trial[25] have indicated that the risk of pelvic sepsis may not be increased by avoiding a temporary ileostomy.

Previous shorter-term analyses of IPAA have demonstrated that bowel function generally is acceptable[4–18]. Importantly, the present analysis has demonstrated that postoperative bowel function remains stable over a 10-year follow-up period for most patients.

The cause of pouchitis is unknown, although it has been shown to be more common in chronic ulcerative colitis than in familial adenomatous polyposis[26], and is more common in patients with extraintestinal manifestations of ulcerative colitis[27], especially primary sclerosing cholangitis[28]. The present analysis demonstrates that the number of patients affected by pouchitis continues to increase with prolonged follow-up. Moreover, it would appear that those who suffer one episode of pouchitis within 2 years of IPAA are likely to have further episodes, whereas those who do not develop pouchitis within the first 2 years are at decreased risk of recurrent pouchitis. In this study the clinical diagnosis of pouchitis was used and it is conceivable that this led to overdiagnosis. Although endoscopic and histological assessment may be helpful in confirming pouchitis, they may also confuse the issue. A pouchitis activity index which combines clinical, endoscopic and histological findings might more accurately predict the true risk of pouchitis. Fortunately, pouchitis typically responds favourably to antibiotic therapy, and in this series was the cause of pouch failure in only three patients.

Small bowel obstruction is observed frequently before ileostomy closure, and remains a potential problem after closure. The proportion of patients suffering small bowel obstruction following IPAA varies between 12 and 24 per cent[29], and it is likely that one of the major determinants of this is the length of follow-up. The total number of patients suffering an episode of small bowel obstruction following IPAA continues to increase significantly for up to 10 years after operation, as might be anticipated after any major abdominal procedure.

Sexual dysfunction following IPAA is uncommon but disturbing. The present study takes into account preoperative sexual dysfunction and indicates that sexual activity improves substantially after long-term follow-up.

Pouch failure increases slightly with prolonged follow-up, and it is preferable to analyse pouch failure as a cumulative risk. While the authors consider a failure rate of 9 per cent at 10 years to be acceptable, especially in light of the alternative surgical procedures available, future patterns of failure will need to be observed. In this series, immediate pouch excision was rare (three of 1310 patients). Pouch failure requiring excision within 2 years was secondary to sepsis and fistula formation whereas pouchitis and Crohn's disease were the primary causes of pouch failure more than 2 years after surgery. The predominant causes of pouch failure in this study, chronic pelvic sepsis, poor functional outcome and Crohn's disease, have also been the foremost aetiologies in two other series[14,16]. Pouch infarction[17] is a most uncommon cause for pouch excision in the authors' experience.

In summary, detailed long-term analysis of 1310 patients with chronic ulcerative colitis undergoing IPAA with a J-shaped reservoir shows that the incidence of postoperative pelvic sepsis decreases significantly with increasing experience. The proportion of patients suffering pouchitis, small bowel obstruction and pouch failure increased with increasing length of follow-up, whereas postoperative sexual dysfunction improved with time. These data support the continued use of IPAA in most patients requiring proctocolectomy for chronic ulcerative colitis.

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Metabolic substrate utilization differs in ileal faecal and urinary reservoirs

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Background Construction of an ileal faecal or urinary reservoir profoundly alters ileal luminal ecology and availability of mucosal metabolic substrates. The aims of this study were to measure mucosal metabolic flux of butyrate and glutamine in histologically normal (control) ileum and to determine the effect of reservoir construction on metabolic fluxes in patients with ileal pouch–anal anastomosis and ileocystoplasty.

Methods Endoscopic biopsy samples were obtained from normal ileum ($n = 10$), ileum of patients with ulcerative colitis ($n = 10$), ileal pouch–anal anastomosis ($n = 7$), ileocystoplasty ($n = 7$) and ileal conduit ($n = 7$). Using a closed microculture technique, biopsy utilization of ^{14}C-labelled butyrate and glutamine was measured as [^{14}C]carbon dioxide production. Biopsy DNA content was measured and [^{14}C]carbon dioxide evolution expressed as picomoles [^{14}C]carbon dioxide per microgram DNA per hour.

Results The metabolic flux of both butyrate and glutamine was reduced in ileal pouch mucosa compared with that of ileal mucosa in patients with ulcerative colitis. In contrast, the metabolic flux of buyrate alone was reduced in ileal mucosa from ileocystoplasty and ileal conduit compared with that in normal ileal mucosa, while the metabolic flux of glutamine remained unchanged.

Conclusion Ileal mucosal metabolic fluxes measured *in vitro* are altered by changing luminal ecology *in vivo*. These changes may affect the health and mucosal integrity of ileum used to construct these reservoirs.

Intestinal mucosal cells metabolize both circulating and luminal metabolic substrates. Circulating glutamine and ketone bodies are the preferred respiratory fuels of ileal mucosa[1], while luminal short-chain fatty acids (SCFAs), the end-product of bacterial fermentation of dietary carbohydrate, provide the principal substrates for oxidation by colonic mucosal cells[2]. Construction of either a faecal or urinary reservoir from distal ileum has profound effects on luminal ecology[3,4]. Changes in luminal metabolic substrate availability may disrupt the metabolic pathways of otherwise healthy mucosa. In the case of ileal pouch–anal anastomosis the healthy equilibrium of ileal ecology is disturbed, a change which may have long-term metabolic and morphological consequences. These changes have been associated with the development of pouchitis[5] which primarily occurs in patients with antecedent ulcerative colitis. The exact aetiology of pouchitis is unknown but alterations in luminal SCFA availability have been implicated in its pathogenesis[6–8]. By contrast, ileal mucosa used to construct a urinary reservoir is exposed to a very different ecology, with complete absence of luminal SCFAs. Changes in mucosal morphology occur soon after reservoir construction[9,10] which may be important for long-term stability of transposed ileal mucosa.

The aims of this study were to determine metabolic substrate utilization in healthy ileal mucosa and to compare this with ileal mucosal metabolism in an ileostomy, ileal pouch anal (faecal) reservoir, ileal (urinary) conduit and ileocystoplasty.

Patients and methods

Control mucosal biopsies were obtained from the terminal ileum of patients undergoing surgical resection for colonic carcinoma ($n = 10$). Control biopsies were taken at least 5 cm from the macroscopic abnormality and all were subsequently histologically normal. Mucosal biopsies were obtained from the terminal ileum of ten patients, free of backwash ileitis, undergoing total colectomy for ulcerative colitis. Biopsies were also taken from the terminal ileum of patients with an established ileostomy for either colonic carcinoma ($n = 8$) or ulcerative colitis ($n = 8$). Biopsies of ileal faecal reservoir mucosa were taken from patients with antecedent ulcerative colitis ($n = 7$) who had a functioning ileal pouch–anal anastomosis without active pouchitis. Endoscopic biopsy specimens were obtained using a standard flexible endoscopic forceps (Olympus FB 13U; Olympus, Tokyo, Japan) and were taken by a surgeon or gastroenterologist of consultant or senior registrar status. Ileal mucosal biopsies were taken from seven patients with ileocystoplasty reservoirs during routine surveillance cystoscopy and from seven patients with an ileal conduit using a flexible cystoscopy forceps (Olympus FB-195X). All patients were in good health with well functioning reservoirs or stomas at the time of biopsy at least 2 years following operation.

Five biopsy specimens were taken from each patient of which two biopsies were used to measure butyrate metabolism, two to measure glutamine metabolism and one reserved for histological examination. Biopsies for metabolic studies were transported in ice-cold sterile RPMI-1640 cell culture medium without glutamine (Gibco, Uxbridge, UK) and assayed immediately. Biopsies were taken from operative specimens by dissection of

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mucosa into 1-mm^3 pieces using a sterile scalpel before transport and immediate assay. All patients gave written informed consent and the protocol was approved by the ethics committee of the Mater Misericordiae Hospital.

Determination of metabolic flux

The metabolic activity of each biopsy specimen was determined by measuring oxidation of [^{14}C]butyrate or [^{14}]glutamine to [^{14}C]carbon dioxide over a 2-h incubation period[11]. Before assay each biopsy was blotted dry and the wet weight recorded. Each biopsy was then placed in a Prolene (Ethicon, Edinburgh, UK) mesh basket attached to a polypropylene suture and transferred to an individual 20-ml Universal glass bottle (Merck, Poole, UK) containing 2-ml sterile RPMI-1640 cell culture medium supplemented with either sodium butyrate 5 mmol/l (Gibco) or L-glutamine 5 mmol/l (Sigma, Poole, UK). These concentrations of glutamine and butyrate were chosen as they have been shown to be within or slightly above the physiological concentration in the human intestine[12,13]. To determine metabolic conversion of either butyrate or glutamine to carbon dioxide, either 3·7 KBq[1-^{14}C] sodium butyrate (specific activity 1·85 MBq) (New England Nuclear, Dreiech, Germany) or 37 KBq L-[U-^{14}C] glutamine (specific activity 1·85 MBq) (Amersham, UK) was added to each Universal bottle containing a biopsy specimen. Released [^{14}C]carbon dioxide was trapped by reaction with sodium hydroxide-saturated filter paper suspended in an opened Eppendorf tube (Eppendorf, Hamburg, Germany) inside each sealed Universal bottle as described by Chapman *et al.*[14]. The quantity of ^{14}[C]carbon dioxide recovered was then determined by liquid scintillation counting. Mucosal biopsies were recovered and frozen at −80°C. Biopsy DNA content was quantified using the standard fluorescent Hoechst dye assay technique[15,16]. Metabolic fluxes for both butyrate and glutamine were then expressed as pmol [^{14}C]carbon dioxide per microgram DNA per hour and pmol ^{14}[C]carbon dioxide per milligram wet weight per hour.

Statistical analysis

All data are expressed as mean(s.e.m.). Duplicate data from each pair of biopsies were consolidated by taking the mean in each case. Comparisons between study groups were performed by one-way analysis of variance with Bonferroni post hoc adjustment. $P \leq 0{\cdot}05$ was considered significant.

Results

Mucosal metabolism in healthy ileal mucosa

There was no significant difference in either butyrate (*Fig. 1a*) or glutamine (*Fig. 1b*) metabolism between control ileal mucosa and ileal mucosa from patients with ulcerative colitis. Mucosal metabolic flux was greater when butyrate rather than glutamine was the available substrate in control ileum and ileum in ulcerative colitis, with a ratio of 6·7 to 1 in respect of control ileal mucosa and 4·9 to 1 in respect of ileal mucosa in ulcerative colitis (*Table 1*).

Mucosal metabolism in ileostomy mucosa

There was no difference in either butyrate (*Fig. 1a*) or glutamine (*Fig. 1b*) metabolism in ileostomy mucosa from patients with either a previous history of colonic carcinoma or ulcerative colitis and control ileal mucosa. Similarly there was no difference in either butyrate (*Fig. 1a*) or glutamine (*Fig. 1b*) metabolism between ileostomy and ileal mucosa from patients with ulcerative colitis. The ratio of butyrate to glutamine metabolic flux was similar in both ileostomy mucosa and control ileal mucosa (*Table 1*).

Mucosal metabolism in ileal pouch mucosa

A significant reduction in both butyrate (*Fig. 1a*) and glutamine (*Fig. 1b*) metabolism was observed in ileal pouch reservoir mucosa when compared with both ileal mucosa and ileostomy mucosa from patients with ulcerative colitis. Nevertheless, the ratio of metabolic fluxes of butyrate and glutamine was preserved (*Table 1*). When wet weight was used as the denominator for expressing metabolic flux, a reduction in the metabolic fluxes of both butyrate and glutamine was also observed (*Table 2*). The

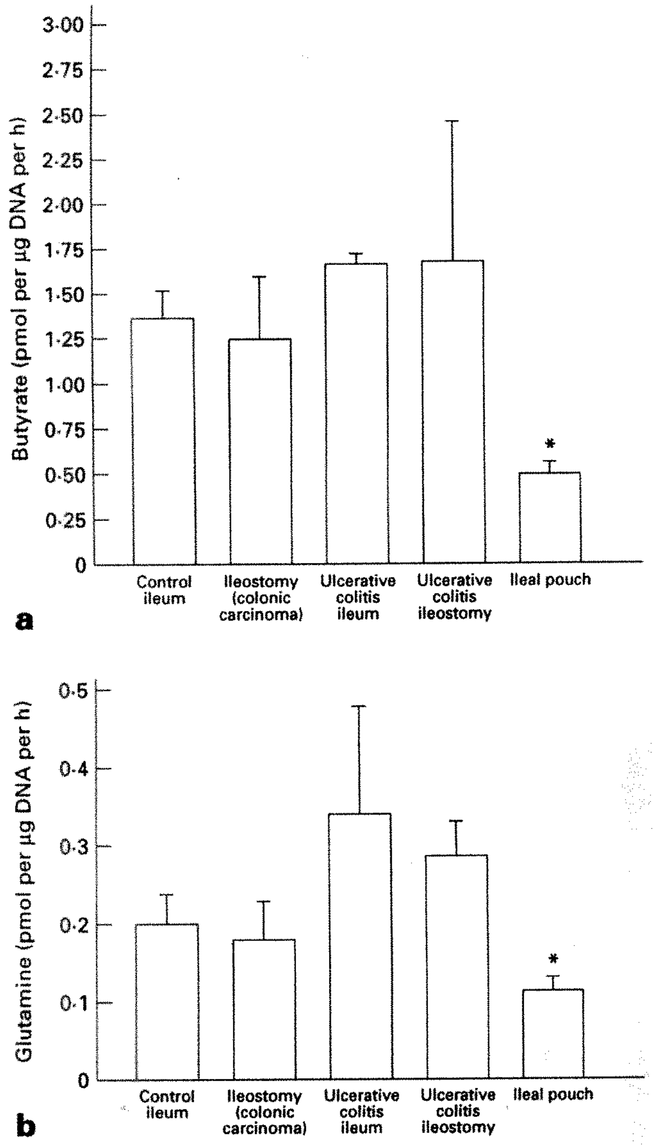

Fig. 1 Ileal mucosal metabolic flux of **a** butyrate and **b** glutamine in normal ileum ($n = 10$), ileostomy for colonic carcinoma ($n = 8$), ileum from patients with ulcerative colitis ($n = 10$), ileostomy for ulcerative colitis ($n = 8$) and ileal pouch mucosa ($n = 7$). Values are mean(s.e.m.). $^*P < 0{\cdot}05$ *versus* ileal mucosa from patients with ulcerative colitis (analysis of variance)

ratio of biopsy DNA content to specimen wet weight was increased in ileal pouch mucosal biopsies compared with that in control ileal mucosa but did not differ from that of ileum in patients with ulcerative colitis (*Table 3*).

Table 1 Ileal mucosal metabolic fluxes of butyrate and glutamine in normal ileum, ileum from patients with ulcerative colitis, ileostomy for bowel carcinoma, ileostomy for ulcerative colitis, ileal pouch faecal reservoir, ileocystoplasty and ileal conduit

	Butyrate (pmol per µg DNA per h)	Glutamine (pmol per µg DNA per h)	Butyrate : glutamine ratio
Normal ileum ($n = 10$)	1·34(0·17)	0·20(0·04)	6·7 : 1
Ulcerative colitis ileum ($n = 10$)	1·65(0·04)	0·34(0·14)	4·9 : 1
Ileostomy for colon carcinoma ($n = 8$)	1·21(0·36)	0·18(0·05)	6·7 : 1
Ileostomy for ulcerative colitis ($n = 8$)	1·66(0·80)	0·29(0·04)	5·7 : 1
Ileal pouch ($n = 7$)	0·47(0·11)*	0·11(0·05)*	4·3 : 1
Ileocystoplasty ($n = 7$)	0·65(0·16)†	0·41(0·19)	1·6 : 1
Ileal conduit ($n = 7$)	0·60(0·19)†	0·19(0·06)	3·2 : 1

Values are mean(s.e.m.). *$P \leq 0{\cdot}05$ *versus* ileal and ileostomy mucosa from patients with ulcerative colitis; †$P \leq 0{\cdot}05$ *versus* normal ileum (analysis of variance)

Table 2 Ileal mucosal flux of butyrate and glutamine in normal ileum, ileum from patients with ulcerative colitis and ileal pouch mucosa

	Butyrate (pmol per mg wet weight per h)	Glutamine (pmol per mg wet weight per h)
Normal ileum ($n = 10$)	3·0(0·3)	0·60(0·09)
Ulcerative colitis ileum ($n = 10$)	4·3(0·7)	0·97(0·27)
Ileal pouch ($n = 7$)	1·8(0·3)*	0·32(0·06)*

Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* ileum from patients with ulcerative colitis (analysis of variance)

Table 3 Ileal mucosal DNA content and biopsy wet weight in normal ileum, ileum from patients with ulcerative colitis and ileal pouch mucosa

	Biopsy wet weight (mg)	µg DNA : mg wet weight ratio
Normal ileum ($n = 10$)	6·6(0·5)	2·4(0·4)
Ulcerative colitis ileum ($n = 10$)	5·3(0·4)	4·9(0·8)*
Ileal pouch ($n = 7$)	4·7(0·3)*	4·4(0·6)*

Values are mean(s.e.m.). *$P \leq 0{\cdot}05$ *versus* normal ileum (analysis of variance)

Metabolism in urinary reservoirs

The metabolic flux of butyrate was reduced in ileal mucosa from ileocystoplasty and ileal conduit compared with that in control ileal mucosa (*Fig. 2a*), while there was no difference in glutamine metabolism between ileal conduit and control ileal mucosa (*Fig. 2b*). There was an increase in glutamine metabolism in ileocystoplasty mucosa but this did not reach statistical significance (*Fig. 2b*).

Histology

Standard light microscopy (haematoxylin and eosin stain) confirmed the presence of intact ileal mucosa in the fifth biopsy taken from each patient. Mucosal morphometry was not performed.

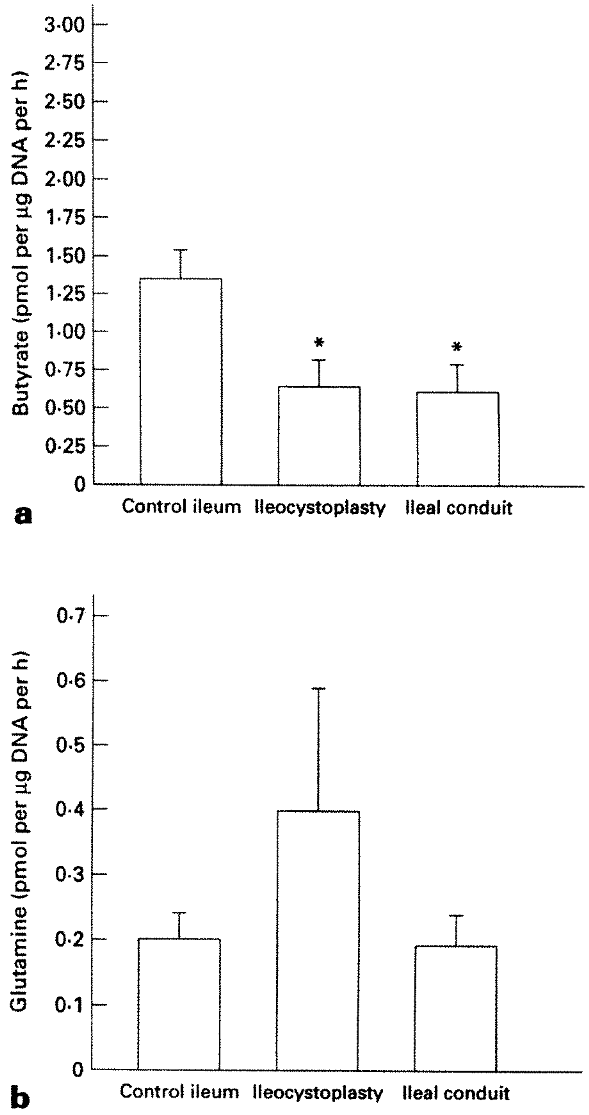

Fig. 2 Ileal mucosal metabolic flux of **a** butyrate and **b** glutamine in normal ileum ($n = 10$), ileocystoplasty ($n = 7$) and ileal conduit ($n = 7$). Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* normal ileal mucosa (analysis of variance)

Discussion

In this study the dramatic effects of *in vivo* ileal reservoir construction on mucosal metabolism of butyrate and glutamine, two of the principal metabolic substrates of ileal mucosa, have been demonstrated *in vitro*. The metabolic flux of both butyrate and glutamine, under controlled conditions of substrate availability, is reduced in ileal mucosa following incorporation into an ileal faecal reservoir whereas the metabolic flux of butyrate alone is reduced in ileal conduit and ileocystoplasty mucosa while that of glutamine is preserved. It was found that the metabolic fluxes of butyrate and glutamine are unchanged in the terminal ileum and established ileostomy of patients with ulcerative colitis when compared with those in control ileum and ileostomy performed for bowel cancer, clearly demonstrating the absence of a panenteric disorder of butyrate metabolism in ulcerative colitis.

Luminal faecal stasis alters the ecology of an ileal pouch which in turn is associated with morphological changes in the mucosa with the appearance of villous atrophy, crypt hyperplasia and chronic inflammation, a combination often described as colonic metaplasia[17–19]. Bacteriological studies have shown that faecal concentrations of total anaerobes, as well as the ratio of total anaerobes to total aerobes in ileal pouch reservoirs are increased compared with those of ileostomy effluent and are comparable to those of the colon[4,6,17,20,21]. With this change to a colonic ecology, increased production of SCFAs *in vivo* might be expected as a result of bacterial fermentation. Indeed SCFA concentrations are increased in ileal pouch effluent compared with those in ileostomy effluent[6] and are similar to luminal concentrations in healthy colon[7].

The present findings differ from those of Chapman *et al.*[22] who claimed evidence of colonic-type metabolic adaptation in ileal pouch faecal reservoir mucosa by showing a decrease in mucosal glutamine metabolism but no change in pouch butyrate metabolism. This discrepancy may be explained by the different methods used to express metabolic flux; Chapman *et al.* used biopsy protein content, whereas biopsy DNA content was used as the denominator for expression of metabolic flux in the present study. This was done to improve assay reproducibility[23]. In this study biopsy DNA:wet weight ratio was increased in pouch ileal mucosa compared with that in control ileal mucosa suggesting the presence of metabolically inert inflammatory cells[24]. However, expression of metabolic fluxes is similar if wet weight is employed as the denominator, indicating that the reduction in mucosal metabolism in ileal pouch mucosa is not solely due to an influx of inflammatory cells but may reflect partial villous atrophy and increased crypt cell proliferation[21].

The modified assay technique used in this study was chosen to most closely reflect *in vivo* mucosal metabolism. The technique allows sampling from macroscopically diseased or macroscopically healthy areas of mucosa and does not require a surgical resection as is required for isolated mucosal cell cultures[2,25]. Furthermore, use of endoscopic biopsies opens the possibility of serial metabolic studies, of particular value in the study of pouchitis. However, the metabolic fluxes measured do reflect total biopsy metabolism, and are subject to differences in biopsy thickness, morphological variation and the presence of submucosal and inflammatory cells[24]. Nevertheless, the technique does provide mucosal cells with more physiological *in vitro* exposure to both luminal and submucosal nutrients than isolated cell culture techniques[2,25].

In previous work[22], metabolic fluxes have been determined in incubations containing both butyrate and glutamine, only one of which was radiolabelled. In the present study the metabolic flux of each substrate was measured in isolation. Whether this explains the different finding in ileal pouch mucosa described by Chapman *et al.*[22] is uncertain. It is possible that a relatively high *in vitro* concentration of unlabelled glutamine may alter oxidation of labelled butyrate. While Chapman *et al.* separately measured the metabolic flux of glucose, in neither study was glucose present in the culture medium as it has little effect on the production of carbon dioxide from either butyrate[2] or glutamine[25].

In contrast to the metabolic effects of ileal pouch faecal reservoir construction, the mucosal metabolic flux of butyrate was reduced in both ileocystoplasty and ileal conduit but that of glutamine was maintained in both and possibly increased in ileocystoplasty. The reduction in butyrate metabolism cannot be explained solely by villous atrophy, which is likely to affect the metabolism of both substrates, but probably reflects decreased luminal substrate availability with downregulation of enzymatic pathways involved in butyrate metabolism. A compensatory increase in the metabolic flux of glutamine is possible in ileocystoplasty.

The reduction in butyrate metabolism in ileal urinary reservoirs may have important implications for the morphological stability of the reservoir mucosa as butyrate is known to stabilize colonic mucosa and to act as a differentiating agent in experimental models[26,27]. Metabolic acidosis, which occurs after enteric urinary diversion[28,29], increases exposure of enteric mucosa to ammonia which, in turn, has been shown to induce morphological changes in the epithelium[30]. In the colon SCFA production reduces exposure of mucosa to ammonia through a reduced luminal pH, which increases conversion of ammonia to the less absorbable ammonium. However, this pathway is not available in ileocystoplasty mucosa. With the loss of the cytoprotective effect of butyrate[31] the present data raise concerns that reduced butyrate metabolism in ileocystoplasty and ileal conduit mucosa may render the mucosa more susceptible to proliferation and neoplastic change[32].

A reduction in the metabolic fluxes of butyrate and glutamine in ileal pouch faecal reservoirs performed for ulcerative colitis was observed which was related to changes in luminal ecology and mucosal morphology and not to a panenteric metabolic abnormality. There was a reduction in the metabolic flux of butyrate in ileal urinary reservoirs related to substrate availability or downregulation of enzymatic pathways involved in butyrate metabolism. These changes in mucosal metabolism may have important implications for the health and integrity of mucosa used to construct these reservoirs.

Acknowledgements

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Extrafascial excision of the rectum for rectal cancer

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Background The fascia propria of the rectum is an upward capsular projection from the superior fascia of the pelvic floor which surrounds the rectum and its mesorectum posteriorly and the fat, blood vessels, nerves and lymphatics in front and laterally. It is postulated that if rectal cancer is contained within the fascia propria and extrafascial excision of the rectum is performed then it would be exceptional for the cancer to recur locally.

Methods A total of 122 consecutive patients with rectal cancer underwent extrafascial excision of the rectum. The operation involved mobilizing the rectum outside its fascia propria and removing not only the rectum and its mesorectum posteriorly but also the fat, blood vessels, nerves and lymphatics in front and laterally. Resection was considered curative unless there were distant metastases or the tumour had involved the resection margins.

Results There was one postoperative death. The cumulative cancer-free survival rate at 5 years was 68 per cent. In 100 patients in whom the operation was considered to be curative, the cumulative cancer-free survival rate was 81 per cent. Eighty-four of these patients were available for a minimum follow-up of 24 (median 73, range 24–193) months. Three (4 per cent) developed local recurrence. In two patients this was at the anastomosis.

Conclusion If the cancer is contained within the fascial tube surrounding the rectum and complete extrafascial excision has been performed, local recurrence will be minimal.

A decade ago a review of the surgical anatomy of the rectum was presented with particular relevance to the technique of rectal excision[1]. Over a period of some years, through literature research and by dissection, a new understanding of the fascia propria of the rectum was gained; it was learned that a gossamer-like membrane surrounds the rectum, enclosing the mesorectum posteriorly and fat, blood vessels, nerves and lymphatics in front and laterally. The fascia propria could be identified at surgery and the rectum mobilized by dissecting outside it, particularly in patients with cancer; it seemed logical that if the rectal cancer was contained within the fascia propria and extrafascial excision had been performed then it would be exceptional, if not impossible, for the cancer to recur locally. Furthermore, the use of the term 'extrafascial excision' would highlight to surgeons and others the vital importance of dissecting in the correct tissue planes in order to avoid recurrent cancer.

Here, the outcome of a consecutive series of patients with rectal cancer in whom the rectum was removed by the extrafascial excision technique is reported.

Patients and methods

The outcome of all patients with rectal cancer personally operated on by one of the authors (G.L.H.) over a 15-year period was studied.

Survival data and the cause of deaths in patients who did not die in hospital were obtained from the New Zealand office of the Registrar of Births, Deaths and Marriages. There was complete follow-up of all patients. Survival was estimated by the method of Kaplan and Meier[2].

Definitions

Operations were considered curative when there was no macroscopic tumour remaining, no distant metastases and the circumferential resection margin (CRM) and distal resection margin were microscopically free of tumour. All other operations were termed 'palliative'.

The lower border of the tumour was measured from the anal verge with a rigid sigmoidoscope with the patient in the left lateral Sims' position. The rectum was divided into lower (0–7 cm), middle (8–11 cm) and upper (12–15 cm) thirds.

The distal margin of clearance was defined as the measured distance from the edge of the tumour at operation in the unstretched rectum. The CRM was identified by inking the fascia propria surrounding the rectum. The CRM was said to be positive when tumour penetrated the margin.

The duration of follow-up was calculated from the date of operation to the date of this review. Routine surveillance colonoscopy was performed within 12 months of surgery. Patients were followed every 3 months for the first year, every 6 months for the second, and once a year thereafter for at least 5 years. A patient was considered free of cancer if the clinical assessment and physical examination including digital rectal examination and sigmoidoscopy was normal. Radiological investigations (chest radiography, abdominal ultrasonography, computed tomography or magnetic resonance imaging) were performed if there was clinical suspicion of recurrent disease.

Local recurrence was defined as disease detected within the pelvis whether or not distant sites of recurrence were present.

Technique of extrafascial excision of the rectum

After mobilization of the sigmoid and descending colon and identification of the left ureter, the superior rectal vessels were identified and separated from the hypogastric nerves. The vessels were then divided 3–4 cm above the pelvic brim (low ligation). The posterior dissection followed the posterior aspect of the superior rectal artery which leads directly on to the fascia propria surrounding the mesorectum. Using long scissors and anterior traction of the rectum, the mesorectum and its surrounding fascia propria was sharply dissected from the presacral fascia. In most patients the junction of the upper rectum with the horizontal rectum was found to be tethered by the rectosacral fascia[3] which was looked for carefully and, when present, divided sharply. The dissection was carried forward posterior to the fascia propria up to the anorectal junction. Attention was then turned to the anterior dissection in which the

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peritoneum was divided just posterior to the seminal vesicles and the dissection carried down on and in front of Denonvilliers' fascia. At approximately 1 cm below the base of the prostate, Denonvilliers' fascia was divided transversely and the dissection carried distally directly in front of the fascia propria as far as the pelvic floor. Having completed the anterior and posterior extrafascial dissections, the fascia propria surrounding the lateral aspects of the rectal tube was identified and the tissues lateral to it were divided sharply paying special attention not to broach the endopelvic fascia enclosing the pelvic autonomic nerve plexus. No formal block dissection of the pelvic lymph nodes was undertaken.

If the tumour was in the upper third of the rectum, at least 5 cm of rectal wall and 5 cm of mesorectum below the tumour margin was removed. If the tumour was in the lower two-thirds of the rectum, most of the rectum together with all the mesorectum was removed. The rectal stump was washed out with 4 per cent povidone–iodine as a precaution against anastomotic recurrence. The same solution was used to irrigate the pelvis after the rectum had been removed. Reconstruction was preferably done by the double-stapling technique[4]. From 1994, if the division of the rectum was within 2–3 cm of the dentate line, a short (6–8-cm limb) colonic pouch was created[5].

Results

Between September 1980 and November 1996, 124 consecutive patients (68 men and 56 women) with a median age of 67 (range 24–92) years were operated on for their first rectal cancer (*Table 1*).

It was possible to resect the tumour in 122 patients (98 per cent); 91 had anterior resection, 19 abdominoperineal resection, ten Hartmann's procedure and two proctocolectomy. In 100 patients the operation was considered to be curative. The median distal clearance margin was 3 (range 0·8–10) cm. The distribution of Dukes stage in the total series is shown in *Table 1*.

Early mortality and morbidity

One patient died 13 days after operation from complications secondary to a bleeding disorder. Anastomotic leakage occurred in nine (10 per cent) of the 91 sphincter-saving operations, all but two occurring from anastomoses in the lower third of the rectum. Seven (8 per cent) had major leaks (one patient had a defunctioning ileostomy) which required laparotomy. There were also two (2 per cent) minor leaks (both patients were defunctioned) causing little systemic upset; both resolved with conservative treatment. There were no deaths as a consequence of anastomotic leak.

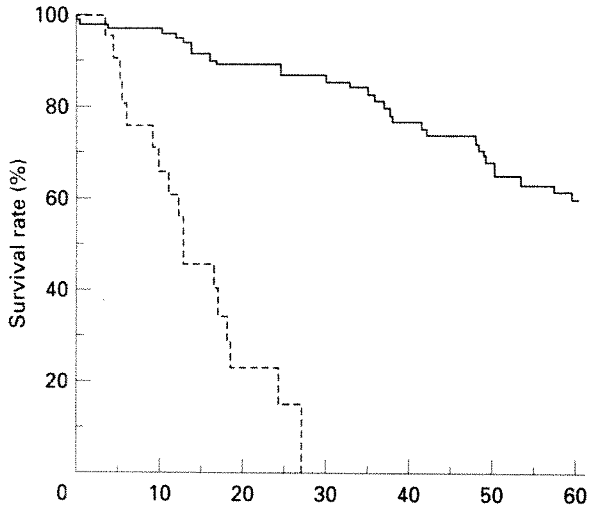
Table 1 Clinical data for 124 patients with rectal cancer

Sex	
M	68 (55)
F	56 (45)
Median age (years) range)	67 (24–92)
Dukes (TNM) stage	
A (T_1N_0–T_2N_0)	25 (20)
B (T_3N_0)	43 (35)
C (T_2N_1–T_3N_1)	38 (31)
'D' (M_1)	18 (15)
Distance of tumour from anal verge (cm)	
0–7	57
8–11	30
12–15	37
Resection rate	122 (98)
Curative operation	100 (82)
Median (range) follow-up (months)	42 (6–193)

Values in parentheses are percentages. TNM, tumour node metastasis

Survival

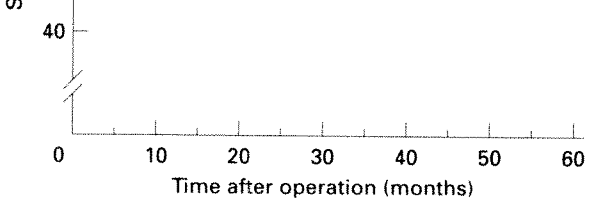
Overall (crude) survival for the curatively and palliatively resected patients is shown in *Fig. 1*. The 5-year cancer-free survival rate for the total series was 68 per cent. The cancer-free survival rate in the 100 patients in the curative group was 81 per cent. *Fig. 2* shows the cancer-free survival rate in these patients according to Dukes stage.



No. at risk

	0	10	20	30	40	50	60
Curative	100	89	75	63	53	41	33
Palliative	22	13	3				

Fig. 1 Overall (crude) 5-year survival in 122 patients who had resection for rectal cancer: ———, curative ($n = 100$); ------, palliative ($n = 22$)



No. at risk

	0	10	20	30	40	50	60
A	25	21	19	15	12	11	7
B	40	38	35	30	25	20	15
C	35	29	20	18	15	10	9

Fig. 2 Cancer-free survival in the 100 patients in the curative group according to Dukes stage: ———, stage A ($n = 25$); — — —, stage B ($n = 40$); -----, stage C ($n = 35$)

Local recurrence

Six patients (6 per cent) developed a local recurrence among 102 patients who were available for a minimum follow-up of 24 months. Three of the recurrences developed in the palliatively resected group of patients and were also associated with systemic recurrence. In the curative group 84 patients (21 with Dukes A, 35 with Dukes B and 28 with Dukes C disease) were available for a minimum follow-up of 24 (median 73, range 24–180) months. Three (4 per cent) of them developed local recurrence. In two patients the recurrence was at the anastomotic line and associated with a very short distal resection margin (less than 1 cm). The other patient had at operation what was thought to be tumour extending beyond the rectum into the pouch of Douglas. However, microscopy of the removed specimen, while indicating tumour extending for 0·9 cm into the perirectal fat, showed a clear CRM.

Adjuvant therapy

Eight of the 84 patients in the curative group had adjuvant therapy comprising preoperative radiotherapy in two with very bulky tumours, postoperative radiotherapy in five (three had extensive infiltration of the mesorectum, two had a perforated carcinoma) and chemoradiotherapy in one. None of these patients developed local recurrence. Three patients have died, 17, 42 and 53 months after operation; the other five are still alive a median of 42 (range 24–85) months after surgery.

Positive resection margins and outcome

Eight (7 per cent) of the 122 patients who underwent extrafascial excision had tumour present at the CRM. In seven patients it was judged at surgery that tumour had extended to the pelvic side walls; three of these patients had liver metastases as well. Six of the eight patients who had a positive CRM died from widespread metastases (three had clinically detectable local recurrence as well) median of 16·2 (range 12–20) months after operation. The other two patients remain clinically free of tumour 19 and 4 months after operation.

Discussion

Local recurrence of cancer in the pelvis occurs in one in five patients treated surgically for rectal cancer[6]. It is rarely cured and most often gives rise to distressing and debilitating symptoms which are difficult to treat. The results of the present study show that if extrafascial excision of the rectum is performed and subsequent histological examination of the removed specimen shows the cancer is contained within the fascia propria then local recurrence is exceptional. Of the 122 patients who underwent extrafascial excision there were six in whom the cancer recurred locally. In three the tumour had already spread beyond the confines of the fascia propria at the time of surgery. Of the other three patients in whom the operation was thought to be curative the tumour recurrence occurred in two at the anastomotic line. In both, the surgical margin was less than 1 cm, which is a clear breach of accepted surgical practice (2 cm is the accepted lower limit[7]). The cause of the local recurrence that occurred in the remaining patient is open to conjecture; presumably residual cancer remained in the pouch of Douglas even though the circumferential resection margin was said to be free of tumour.

Other surgeons have also reported local recurrence rates after curative surgery for rectal cancer of around 5 per cent and with overall cure rates of about 80 per cent[8,9]. They have usually attributed these results to the fact that they performed total mesorectal excision (TME)[10]. The importance of adequate excision of the mesorectum is highlighted by the pathological studies demonstrating microscopic tumour deposits beyond the distal extent of intramural spread in up to 25 per cent of cases[10–12]. Indeed, TME has been endorsed as the new standard for the surgical treatment of rectal cancer in Norway and Sweden[13]. Although it is not always clearly stated, most detailed descriptions of TME indicate that the dissection is conducted in the extrafascial plane and most surgeons applying TME principles are actually performing extrafascial excision. Heald, who pioneered the concept of removing the whole mesorectum as a technique for preventing local recurrence, stressed the importance of dissecting in the so-called 'Holy Plane', which is in fact the areolar tissue just outside the fascia propria[14].

The results of the present series also shed light on the difficulties raised by studies in which the presence of cancer at the CRM has been noted. Studies in which standard surgical techniques were applied have shown that the CRM is positive in 20–25 per cent of patients judged at surgery to have had macroscopically complete excision and that a 'positive CRM' is highly predictable of local recurrence[15–18]. The present study shows that a positive CRM after extrafascial excision is less common (7 per cent) and is almost invariably associated with systemic disease and poor prognosis. These findings are in accord with those of Cawthorn *et al.*[19], who demonstrated a similar association between a positive CRM and systemic recurrence (not local recurrence) after TME.

It is proposed that the operation in which the rectum is removed in the anatomical plane outside the fascia propria should be called by its proper name, extrafascial excision. Surgeons usually regard alimentary tract mesenteries as posterior rather than circumferential structures, and the term 'extrafascial excision' highlights the necessity of performing a circumferential dissection outside the fascia propria in order to keep the incidence of local recurrence at the lowest possible level. Understanding the concept that rectal cancer confined within the fascia propria of the rectum can be removed with a very low local recurrence rate also has important implications and challenges for radiologists and oncologists.

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Novel approach to combined defaecation and micturition disorders with rectovaginovesicopexy

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Background This study was conducted to investigate the results of rectovaginovesicopexy (RVVP) in patients with combined defaecation and micturition disorders. RVVP was developed from a standard procedure for different forms of defaecation disorders (the rectovaginopexy (RVP)). It is only a limited extension to the RVP and results in elevation of all three pelvic compartments.

Methods In a consecutive series of 25 patients the effects or RVVP were evaluated prospectively. Information about the clinical history and results was obtained by a standard questionnaire filled out before and 3 and 12 months after operation. Dynamic defaecography was performed before and 3 months after RVVP. Before operation urodynamic studies were conducted.

Results RVVP improved constipation (14 of 18 patients improved, $P = 0{\cdot}001$), faecal incontinence (11 of 16 patients improved, $P = 0{\cdot}005$) and dysfunctional voiding (ten of 16 patients improved, $P = 0{\cdot}07$) without induction of these disorders. Overall urinary incontinence improved in 11 of 22 patients ($P = 0{\cdot}18$), with deterioration of urinary incontinence in three and induction of urinary incontinence in two of the patients. Patients with isolated urinary stress incontinence fared better (eight of 13 patients improved) than those with mixed urinary incontinence.

Conclusion RVVP provides satisfactory improvement of combined defaecation and micturition disorders. The benefits of a limited extension of the RVP seem to outweigh potential side-effects such as deterioration or *de novo* defaecation or micturition disorders.

Disorders of anorectal function should not be considered in isolation but are part of a spectrum of pelvic floor dysfunction[1,2]. Many authors have drawn attention to the combined occurrence of anorectal, gynaecological and urological symptoms[3–9]. This coexistence of symptoms is not surprising in view of the close anatomical relation and common innervation of the pelvic floor structures and shared susceptibility to damage from childbirth, chronic straining at stool and hormonal changes associated with the menopause[1].

Previous experience in the treatment of patients with the combination of constipation and faecal incontinence by rectovaginopexy (RVP)[10] revealed concomitant relief of urinary incontinence in some patients and deterioration in others. The reason for this variable effect on urinary incontinence was unclear. In this study patients with different combinations of defaecation and micturition disorders and anatomical abnormalities (rectocele, internal rectal intussusception, enterocele, cystocele and/or vaginal vault or uterovaginal prolapse) were treated by rectovaginovesicopexy (RVVP) to elevate all three compartments of the female pelvis. RVVP should accomplish elevation of the vesicourethral junction and improve urinary incontinence as a result of abdominal pressure transmission to the vesicourethral junction. The main purpose of the study was to investigate the effect of addition of vesicopexy to RVP on disordered defaecation and coexisting micturition problems.

Patients and methods

Clinical assessment

From March 1993 to March 1994, a consecutive series of 25 patients with a mean(s.d.) age of 54(11) (range 38–70) years underwent RVVP. All operations were supervised or performed by one of the authors (L.W.M.J.). Information about the clinical history was obtained by a standard questionnaire before and 3 and 12 months after operation.

Constipation was divided into four categories to quantify the effect of the operation. In addition, constipation was scored according to the definition of Drossman *et al.*[11] to make comparisons with the literature[12–14]. Patients with grade 3 and 4 constipation were considered constipated according to the Drossman criteria.

Faecal continence was graded according to Browning and Parks[15] into four categories.

Dysfunctional voiding and urinary continence were divided into four categories as well. Based on the history as well as urodynamic physiology studies, patients were classified as having urge or stress urinary incontinence or both. The clinical history concerning urinary incontinence was compared with urodynamic findings. In all cases the indication for RVVP was determined by a surgeon, a urologist and a gynaecologist. All patients had had previous pelvic surgery (mean 1·7 operations). Constipation was the indication for surgery in ten patients and faecal incontinence in 15. Overall, 18 patients were constipated, ten of whom reported constipation as the primary symptom. The other eight had constipation in combination with faecal incontinence as the main symptom (*Table 1*). In 22 patients urinary incontinence was a secondary symptom. Symptoms leading to surgery were accompanied by abnormal findings at physical examination (*Table 2*) and anatomical abnormalities on dynamic defaecography (rectocele, internal rectal intussusception, enterocele or combined abnormalities).

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Table 1 Main and secondary symptoms before rectovaginovesicopexy

Main symptom	No. of patients	Secondary symptoms	No. of patients
Constipation*	10	Urinary incontinence	2
		Urinary incontinence and dysfunctional voiding	5
		Dysfunctional voiding	2
		Faecal incontinence	1
Faecal incontinence	15	Constipation, urinary incontinence and dysfunctional voiding	5
		Constipation and urinary incontinence	2
		Constipation and dysfunctional voiding	1
		Urinary incontinence and dysfunctional voiding	3
		Urinary incontinence	4

*According to the definition of Drossman *et al.*[11]

Table 2 Findings at physical examination before rectovaginovesicopexy

	No. of patients
Cystocele*	22
Vaginal vault prolapse*	7
Uterovaginal prolapse*	4
Rectocele†	20

*Determined by the gynaecologist; †determined by the surgeon

Dynamic defaecography

Dynamic defaecography, as described by Mahieu *et al.*[16,17] was also performed before and 3 months after RVVP. Data were obtained by analysing videotapes and were reviewed by a panel unaware of patients' symptoms and whether defaecograms were made before or after RVVP. As well as rectal barium contrast and contrast coating of the vagina, in all cases, oral contrast was given to detect an enterocele. Depth of a rectocele was classified according to Shorvon *et al.*[18] and measured as the maximum depth of the anterior bulge beyond the expected and extrapolated line of the anterior rectal wall. Rectocele, intussusception and enterocele were divided into three grades (*Table 3*). Protrusion of an intussusception beyond the anal canal was called rectal prolapse. Patients with signs of a non-relaxing puborectalis syndrome were excluded based on both clinical symptoms and radiographic findings.

Urodynamic physiology studies

Urodynamic investigations were performed before RVVP by filling and diuresis cystometry with pressure flow studies[19]. Genuine stress incontinence (GSI), detrusor overactivity/measured urge incontinence (MUI), urethral instability, maximum flow rate, detrusor pressure during voiding, urethral resistance and maximum urethral closing pressure (UCP) were determined.

Surgical procedure

The RVVP evolved out of the rectovaginopexy (RVP)[10]. The technique, as described in detail below, aims at avoiding damage to the hypogastric plexus and pelvic autonomic nerves by dissection of the peritoneum only, without mobilization of the dorsolateral side of the rectum and with preservation of the lateral ligaments.

Table 3 Effect of rectovaginovesicopexy on size of rectocele, internal rectal intussusception and enterocele

	Before RVVP	3 months after RVVP	*P*§
Rectocele*			
None	2	11	0·0004
Grade I	13	9	
Grade II	8	1	
Grade III	1	0	
Unknown	1	4	
Internal intussusception†			
None	16	21	0·01
Grade I	2	0	
Grade II	3	0	
Grade III	3	0	
Unknown	1	4	
Enterocele‡			
None	14	20	0·01
Grade I	2	0	
Grade II	4	0	
Grade III	4	1	
Unknown	1	4	

*According to Shorvon *et al.*[18]: grade 1, less than 2 cm; grade II, 2 cm or more and less than 4 cm; grade III, 4 cm or greater. †Grade I, above the puborectal sling; grade II, as low as the puborectal sling; grade III, into the anal canal. ‡Grade I, above the puborectal sling; grade II, as low as the puborectal sling; grade III, down to the perineum. RVVP, rectovaginovesicopexy. §Wilcoxon paired signed rank test

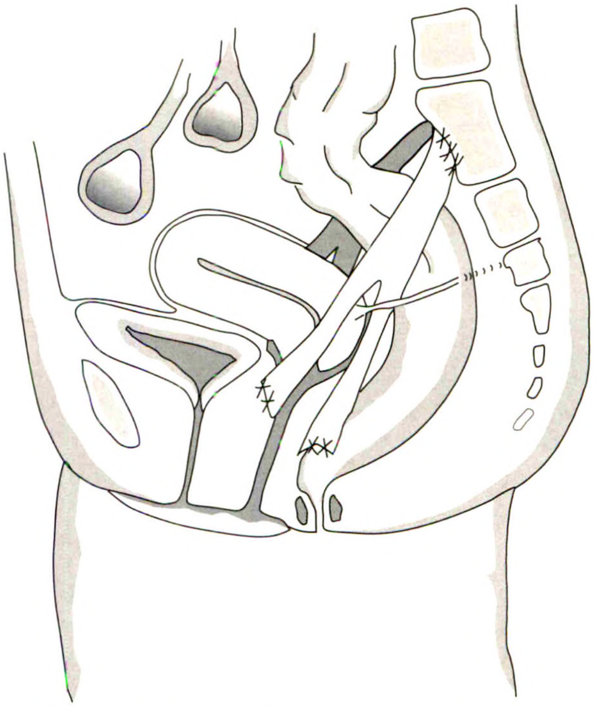

Fig. 1 Schematic representation of the polytetrafluoroethylene strip fixed to the promontory with fixation of the dorsal arms of the strip to the anterolateral side of the rectum. The ventral arms of the strip are fixed to the dorsal side of the elevated bladder

The operation is performed through a midline laparotomy. The peritoneum on both sides of the rectum and in the rectouterine pouch is incised and the peritoneum is dissected from the underlying structures in lateral and caudal directions. Thereby, no nerves are endangered and both ureters are left undisturbed. The space between the rectum and vagina is dissected, in the avascular plane, down to the level of the pelvic floor. Hereafter, the whole rectum is mobile and the part of the rectum originally situated at the bottom of the pouch of Douglas can be brought up to the promontory. The lateral ligaments are not divided.

Subsequently the space between the vagina and bladder is dissected. A small hole is made by blunt dissection between the rectum and the promontory. A polytetrafluoroethylene (PTFE) (GORE-TEX; W.L. Gore, Woking, UK) strip of 20 × 3 cm is fixed in the middle to the promontory with non-absorbable sutures. The free ends of the strip are divided, creating four arms. The PTFE strips are not placed through the broad ligament. The dorsal arms of the strip run posterior and the ventral arms anterior to the broad ligament. Uterine vessels are not divided. The two dorsal arms of the strip are sutured to the antero(lateral) side of the stretched rectum as low as possible (i.e. well below the pouch of Douglas). Closure of the space between the rectum and vagina, to prevent or treat a uterine or vaginal prolapse, is achieved by suturing the insertions of the uterosacral ligaments to the splitting point of the PTFE strips with non-absorbable sutures. The two other arms of the PTFE strips are fixed to the dorsal side of the elevated bladder. A suction drain is placed to prevent haematoma formation. The peritoneum is trimmed and reefed by a continuing running resorbable suture to cover the PTFE strip (*Fig. 1*).

Statistical analysis

Data not normally distributed were compared using Wilcoxon's paired signed rank test. $P < 0.05$ was considered statistically significant.

Results

Clinical data

The effect of RVVP on constipation in all 25 patients is shown in *Fig. 2*. Some 12 months after RVVP, constipation was completely abolished in nine of 19 patients. One patient developed grade 2 constipation. According to the definition of Drossman *et al.*[11], constipation was cured in 14 of 18 patients ($P = 0.001$) and no patient developed constipation.

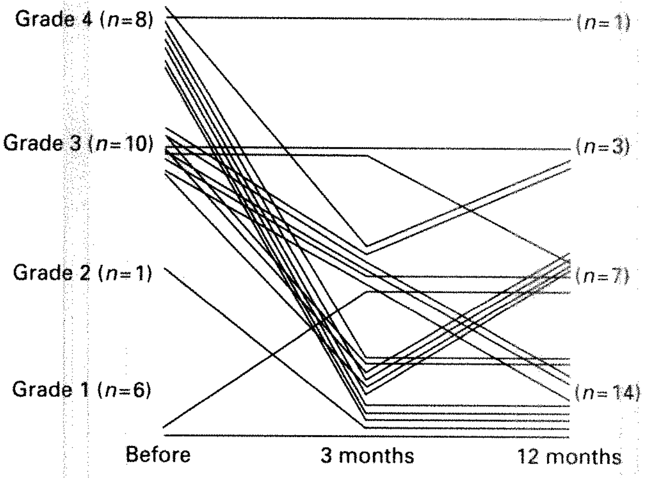

Fig. 2 Effect of rectovaginovesicopexy on constipation. Grade 1, not constipated; grade 2, constipated once in a while (less than 25 per cent of the time); grade 3, constipated frequently (25–75 per cent of the time); grade 4, always constipated (more than 75 per cent of the time). According to the definition of Drossman *et al.*[11], only patients with grades 3 and 4 are constipated

Fig. 3 illustrates the effect of RVVP on faecal incontinence. In 11 of 16 patients faecal continence improved ($P = 0.005$).

RVVP had a positive, although not significant, effect on dysfunctional urinary voiding 12 months after operation ($P = 0.07$). At 12 months the feeling of dysfunctional voiding was abolished completely in seven of 16 patients, diminished in three, unchanged in three and in three other dysfunctional voiding deteriorated (*Fig. 4*).

RVVP had a variable effect on urinary incontinence ($P = 0.18$ at 12 months). At 1 year after RVVP, six of 22 patients were completely continent of urine. Urinary incontinence improved in a further five patients, was unchanged in eight and deteriorated in three. Two patients developed some degree of urinary incontinence (*Fig. 5*). The patients with an isolated history of urinary stress incontinence (USI) fared better than those with

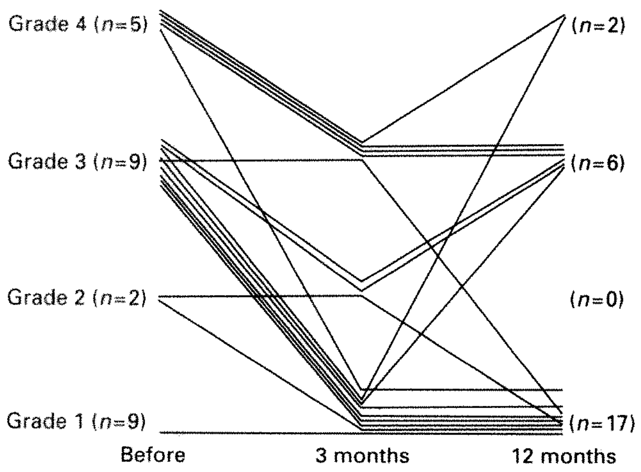

Fig. 3 Effect of rectovaginovesicopexy on faecal incontinence. Grade 1, completely continent; grade 2, continent to stools but incontinent to flatus; grade 3, incontinent to liquid stools and flatus but normally continent to solids; grade 4, completely incontinent

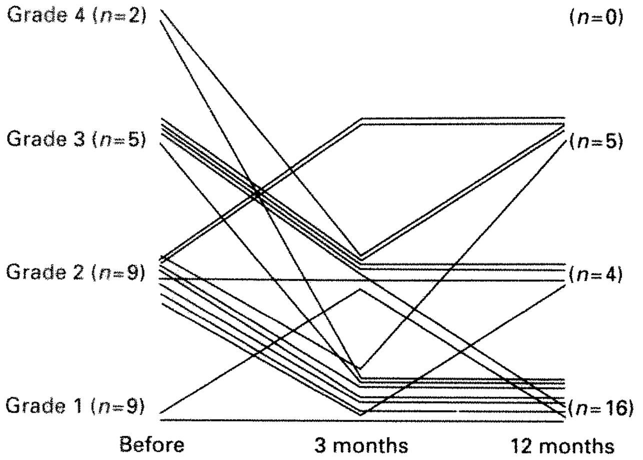

Fig. 4 Effect of rectovaginovesicopexy on dysfunctional voiding. Grade 1, normal feeling of bladder emptying with normal stream; grade 2, once in a while squeezing at micturition and a feeling of incomplete bladder emptying; grade 3, frequent squeezing at micturition with bladder emptying in several attempts; grade 4, always squeezing and always a feeling of incomplete bladder emptying, or self-catheterizing

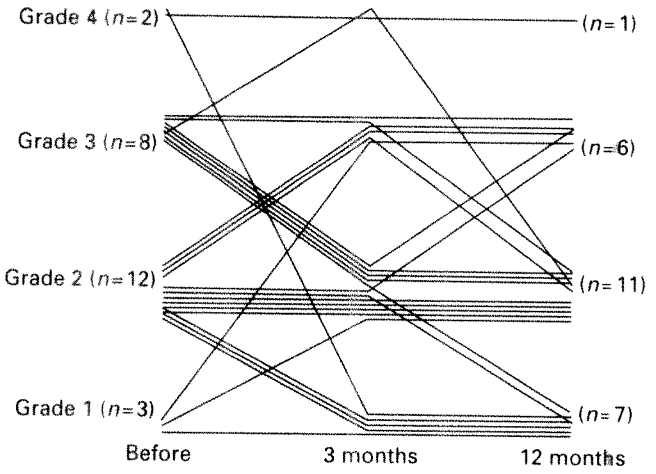

Fig. 5 Effect of rectovaginovesicopexy on urinary incontinence. Grade 1, no urinary incontinence; grade 2, loss of small amounts of urine; grade 3, regular loss of larger volumes (more than 5 pads five per day); grade 4, complete urinary incontinence

both USI and a history of urinary urge incontinence (UUI). In 13 patients with USI only, urinary incontinence improved in eight, whereas in a further eight patients with both USI and UUI only two improved. Urinary incontinence improved in one patient with UUI only. Of three patients without urinary incontinence, one remained completely continent to urine, one developed grade 2 USI and one grade 3 UUI.

Dynamic defaecography

Before operation a rectocele was found in 20 patients, intussusception in eight and enterocele in ten. After RVVP, these values decreased to ten, zero and one respectively (*Table 3*). Six of the remaining ten rectoceles were smaller than before RVVP and four did not change in size (all grade I rectoceles). Only one patient had a rectocele greater than 2 cm after RVVP. In four patients preoperative and/or postoperative defaecograms were lacking because they refused to undergo the procedure.

Urodynamic physiology studies

Preoperative urodynamic physiology studies were available for 21 patients. Clinical history was compared with urodynamic findings. In 13 patients urodynamic findings of the presence or absence of stress incontinence were concordant with the history. Eight patients had USI without GSI. In 16 patients urodynamic findings concerning the presence or absence of urge incontinence were concordant with the history. Four patients had a history of UUI without urge incontinence at urodynamic investigation (further described as MUI), and one had MUI without a history of UUI.

At urodynamic investigation seven patients had GSI; four showed improvement after RVVP, in two urinary incontinence did not alter and in one symptoms deteriorated. Four patients with MUI were identified; two improved and in the other two urinary incontinence deteriorated. In the two patients with GSI as well as MUI, urinary incontinence did not improve. In eight patients neither GSI nor MUI was determined, although seven of these patients had a history of urinary incontinence. Maximum UCP before operation did not have any predictive value in determining patients who ultimately had no relief of urinary incontinence.

Discussion

This pilot study investigated not only the effect of RVVP on defaecation disorders but focused specifically on the effect on frequently encountered accompanying micturition disorders. RVVP is only a limited extension of the RVP (the authors' standard procedure for different forms of defaecation disorders) with concomitant vesicopexy resulting in elevation of all three pelvic compartments. The question addressed was whether the benefits of this limited extension of RVP in terms of improvement of micturition disorders outweighed potential side-effects such as deterioration of already disordered defaecation or micturition and/or the induction of *de novo* micturition disorders. To the authors' knowledge no previous study has focused on such an integrated operative approach to defaecation and micturition disorders.

RVVP improved constipation in 14 of 18 patients. No patient developed constipation. This compares favourably with other types of abdominal rectopexy, especially when the lateral ligaments of the rectum are divided[12,20,21]. In 11 of 16 patients faecal incontinence improved and in eight of the 16 faecal incontinence was cured. No patient developed faecal incontinence. Improvement of faecal incontinence after rectopexy as reported in the literature ranges from 50 to 90 per cent; alterations in, or coexistence of, urinary incontinence is not mentioned[13,20,22–24].

Although dysfunctional voiding improved in ten of 16 patients and urinary incontinence in 11 of 22, three of the patients reported deterioration of urinary incontinence, whereas two developed incontinence. Patients with stress incontinence fared better (eight of 13 with USI and four of seven with GSI improved) than those with combined stress and urge incontinence (two of eight improved). The patient's history appears to be unreliable in determining GSI or detrusor overactivity[25]. In the present patients the diagnosis of both USI and UUI was made more often on the history than by urodynamic assessment showing GSI or detrusor overactivity. Urodynamic assessment is considered as the criterion standard in determining stress or urge incontinence although urodynamic assessment is a rather unphysiological reflection of a moment in an incontinent patient's life[25,26]. The fact that in seven patients neither GSI nor detrusor overactivity was demonstrated despite a clear history of loss of urine is an illustration of this problem.

Comparison of the effects of RVVP on dysfunctional voiding and urinary incontinence with surgical procedures for USI that address the bladder compartment only is hampered by differences in patient population. Studies on the effect of surgical treatment of urinary incontinence usually do not mention concomitant symptoms, such as dysfunctional voiding, faecal incontinence or constipation. The Marshall–Marchetti–Krantz procedure, Burch colposuspension and needle suspensions (Stamey–Pereyra) for GSI have a cure rate of 70–90 per cent. However, these procedures are accompanied by *de novo* incontinence as well. *De novo* voiding disorders and *de novo* detrusor instability are reported in 6–12 and 6–11 per cent of patients respectively[27]. RVVP did not induce voiding disorders, although in three of 16 patients the feeling of dysfunctional voiding was aggravated by one grade. *De* *novo* detrusor instabilities could not be determined because of lack of postoperative urodynamic physiology studies.

Dynamic defaecography made it clear that, 3 months after RVVP, the anatomy of the posterior and middle compartment of the pelvis was grossly restored (*Table 3*). Besides nine grade I rectoceles, which is within normal physiological range[18,28], only one grade II rectocele and one enterocele were noticed. None of the contrast-coated vaginas showed any sign of vaginal vault or uterovaginal prolapse or of a cystocele during dynamic defaecography.

In conclusion, RVVP provides improvement of constipation, faecal continence and dysfunctional voiding, without induction of these symptoms. A limited extension to the RVP improved patients' urinary incontinence in half of the cases, with an acceptable degree of deterioration of urinary incontinence. Prospective randomized studies comparing the effect of RVP with RVVP or of RVVP with RVP in combination with a Burch colposuspension are needed to elucidate further the role of an integrated approach to patients with combined urological and anorectal symptoms.

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Proinflammatory mediator activity, endogenous antagonists and the systemic inflammatory response in intra-abdominal sepsis

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Background Severe intra-abdominal sepsis continues to carry a high mortality rate. The physiological response to sepsis in this condition and its relationship with proinflammatory mediators and their endogenous antagonists require further clarification.

Methods Fifty-seven patients were stratified by Acute Physiology And Chronic Health Evaluation (APACHE) II score at the time of admission to an intensive care unit (group 1, score of less than 20; group 2, score of 20 or more). Serial measurements of clinical and immunological variables were made.

Results Non-survivors from group 2 had a raised acute physiology score ($P = 0{\cdot}01$), a higher peak serum interleukin (IL) 6 concentration ($P = 0{\cdot}03$) and a depressed level of endogenous immunoglobulin (Ig) G class antiendotoxin core antibody ($P = 0{\cdot}005$). In group 1, although organ failure score increased progressively in non-survivors, physiology score and peak IL-6 level were similar to those in survivors, and endogenous IgG class antiendotoxin core antibody titre rose ($P = 0{\cdot}02$). In both groups IL-1 and tumour necrosis factor α were detected infrequently, but their natural antagonists were present in much higher concentrations in both survivors and non-survivors. Levels of C-reactive protein were raised in both but were not significantly different between survivors and non-survivors.

Conclusion During the development of organ failure and death, the pattern of proinflammatory mediators and their endogenous antagonists can vary markedly and may in part be determined by the extent of the initial physiological disturbance.

Despite current supportive care, correct surgical practice and antimicrobial therapy, the mortality rate from severe intra-abdominal sepsis remains at 40–50 per cent[1–3]. At present it seems that the major threat to survival comes not from the underlying infection but from the progressive derangement of organ function as a consequence of the systemic inflammatory response and its sequelae[4]. The severity of the acute physiological derangement associated with sepsis acts as an independent risk factor for mortality in intra-abdominal infection[5,6].

The administration of endotoxin to humans can induce the clinical signs associated with the sepsis syndrome[7], these manifestations being related to increased production of endogenous cytokines, which in turn can reproduce aspects of sepsis syndrome[8,9]. The cytokine responses to endotoxin vary considerably between individuals[10,11], and may in turn influence the degree of the systemic inflammatory response. Although raised levels of circulating endotoxin and the proinflammatory cytokines interleukin (IL) 1β, tumour necrosis factor (TNF) α and IL-6 correlate to some degree with the severity and outcome of sepsis[12–15], the prognostic usefulness of circulating cytokine concentrations is often less than that of clinical variables[3]. In addition, blockade of proinflammatory mediators by passive immunization against endotoxin[16], TNF-α[17] and IL-1β[18] has failed to improve survival in patients with sepsis, despite the promise of animal studies[9,19,20]. Delay to treatment and the presence of naturally occurring antagonists, such as endogenous antiendotoxin antibodies, soluble TNF receptor and IL-1 receptor antagonist (IL-1ra), may partially explain such results[21–23].

The extent to which the interplay between proinflammatory mediators and endotoxin with their naturally occurring antagonists influences outcome is unknown and it is uncertain whether the interplay corresponds with the level of physiological disturbance. The authors have previously reported a large heterogeneous group of patients with sepsis syndrome who were admitted to intensive care units (ICUs)[24]. This paper examines further the subgroup of patients with intra-abdominal infection. Patients were stratified into two risk categories according to Acute Physiology And Chronic Health Evaluation (APACHE) II score[25], so that the importance of proinflammatory and anti-inflammatory events in relation to outcome could be assessed at the same time as recognizing confounding factors such as age, pre-existing medical conditions and disease severity. The present study examines the relationship between outcome and circulating levels of plasma endotoxin, IL-6 and C-reactive protein (CRP), IL-1β and mediator antagonists, the significance of acute physiology and organ failure scores, and 30-day mortality.

Patients and methods

Patients

A group of 57 patients in ICUs with sepsis syndrome of abdominal origin were studied over a 16-month period in five

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units. Patients were enrolled if there was clinical or radiological suspicion of intra-abdominal infection (this being confirmed at laparotomy) and if they fulfilled all the criteria for sepsis syndrome: (1) hyperthermia (temperature greater than 38°C) or hypothermia (less than 35·5°C); (2) tachycardia (more than 90 beats per min in the absence of β-blockade); (3) tachypnoea (more than 20 breaths per min) or requiring mechanical ventilation; and (4) evidence of failure of one or more end-organs (defined as a plasma lactate concentration greater than 1·2 mmol l^{-1} or base deficit above 5 mmol l^{-1} or systemic vascular resistance lower than 800 dyn s/cm^5; ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (P_{aO_2}/F_{iO_2}) lower than 30 kPa or P_{aO_2} less than 9·3 kPa; urine output less than 120 ml over 4 h; Glasgow Coma Score less than 15 in the absence of a neurological lesion[24,26]).

Approval for the study was granted by each centre's ethical committee and written informed consent was obtained from the patient or a relative. Patients were followed until death or for 30 days. Severity of illness was scored on enrolment using the APACHE II system[27]. Organ failure was assessed daily for 7 days and at day 10 using an organ failure score[28]. Terms employed for the description of intra-abdominal infection and types are those recommended and defined by the Joint Working Party of the Surgical Infection Society[25].

Patient stratification

Patients were stratified using the APACHE II score. Patients in group 1 ($n = 24$) had an APACHE II score of less than 20 and those in group 2 ($n = 33$) had a score of 20 or more at study entry. The predicted mortality rate of these two groups, weighted for abdominal infection, was less than 58 per cent for group 1 and more than 64 per cent for group 2[27].

Blood sampling protocol

Blood was drawn daily for 7 days and on day 10 by venepuncture or from an indwelling arterial line. Blood (20 ml) was collected for aerobic and anaerobic culture at two time points in the first 24 h. Blood for endotoxin and endogenous antiendotoxin core antibody (EndoCAb) measurements was drawn into heparinized endotoxin-free tubes, centrifuged and the resulting plasma stored at −20°C. Blood for cytokine and CRP measurements was drawn at study entry and on consecutive days for 1 week and again on day 10. Blood was allowed to clot in glass tubes at room temperature, centrifuged and the resulting serum was stored at −20°C[24].

Laboratory assays

IL-1ra was measured by enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, Minnesota, USA) according to the manufacturer's instructions. Type I soluble TNF receptor (sTNFr55) was detected by sandwich ELISA (anti-sTNFr55 antibodies were kindly donated by Dr W Buurmann), as described previously[24]. Plasma endotoxin concentrations were determined with the Coatest Endotoxin (Chromogenic) test kit (Chromogenix; Quadratech, Epsom, UK). The assay was sensitive to levels of endotoxin over 0·05 units ml^{-1}. Immunoglobulin (Ig) G and IgM EndoCAb were measured with an ELISA as described previously[21,24]. Depletion of EndoCAb was defined as lower than the tenth centile of the value in a group of healthy adult blood donors. The tenth centile for IgG EndoCAb was 33·7 IgG median units (GMU) per ml, and for IgM EndoCAb it was 39·7 IgM median units per ml.

CRP was measured by a standard ELISA (DAKO; Ely, Cambridgeshire, UK), samples being diluted 1:30 000. The ELISA for IL-6 used a murine monoclonal antihuman IL-6 antibody (Boehringer-Mannheim, Mannheim, Germany) and a goat polyclonal antihuman IL-6 antibody (British Biotechnology, Abingdon, UK), followed by a peroxidase-conjugated antigoat IgG (Sigma, Poole, UK).

Statistical analysis

Results are given as the mean(s.e.m.). Group frequencies were compared with the χ^2 test. Continuous data were compared with the Mann–Whitney *U* test and Scheffé's method for multiple comparisons was used to determine the significance of differences at individual time points. To assess the influence of variables on overall survival, time-dependent covariates were entered into the Cox regression model. Differences were considered significant when the probability of their arising by random sampling error was less than 1 in 20 ($P < 0·05$).

Results

Patients

The 57 patients (31 men and 26 women) had a mean(s.e.m.) age of 65(2·1) years. On admission to the ICU the mean(s.e.m.) APACHE II score was 22(1) and the overall mortality rate was 58 per cent (33 of 57 patients). Non-survivors were not significantly older than survivors (68(3) *versus* 62(3) years; $P = 0·09$, Mann–Whitney *U* test), but their APACHE II scores were significantly higher (24(1) *versus* 20(1); $P = 0·025$, Mann–Whitney *U* test). Non-survivors were more likely to have been shocked before study entry (25 of 33 *versus* 11 of 24 patients, $P < 0·05$). At the time of admission, serum creatinine levels were higher in non-survivors (192·1(11·6) *versus* 146·9(25·1) μmol l^{-1}; $P = 0·02$, Mann–Whitney *U* test); serum albumin and bilirubin levels were similar in survivors and non-survivors, as was the prothrombin time and the incidence of malignancy (*Table 1*).

Operative findings

The stomach and duodenum were identified more frequently at laparotomy as the source of intra-abdominal infection in non-survivors (15 of 33 *versus* four of 24 in survivors, $P < 0·05$). The remaining anatomical origins of sepsis occurred with similar frequency. All patients underwent an operative procedure for intra-abdominal infection. No clear differences emerged with regard to the bacteriology of primary cultures from the peritoneal

Table 1 Patient characteristics

	Total ($n = 57$)	Survivors ($n = 24$)	Non-survivors ($n = 33$)	*P*
Sex ratio (M:F)	31:26	13:11	18:15	<0·5‡
Age (years)*	65·4(2·1)	62·4(3·3)	67·6(2·8)	0·09†
APACHE II score*	22·1(0·8)	19·7(1·1)	23·8(1·1)	0·025†
Shock before study	36	11	25	<0·05‡
Time from diagnosis to index procedure (h)*	87·9(33·4)	127·9(69·5)	52·8(13·7)	0·23†
Time from diagnosis to study entry (h)*	132·9(43·7)	172·6(85·8)	96·7(30·9)	0·44†
Malignancy	12	4	8	<0·25‡
Albumin (g l^{-1})*	26·1(1·4)	26·2(1·2)	26·0(2·5)	0·47†
Bilirubin (μmol l^{-1})*	23·7(2·3)	22·6(32·9)	24·7(3·6)	0·41†
Prothrombin time (s)*	23·7(2·4)	19·2(1·5)	27·2(4·9)	0·71†
Creatinine (μmol l^{-1})*	172·9(14·8)	146·9(25·1)	192·1(11·6)	0·02†
Haematocrit (%)*	35·6(1·3)	35·0(1·8)	36·0(1·7)	0·69†
Operating time for index procedure (min)*	121·7(7·9)	131·2(12·9)	115·0(9·4)	0·73†
Patients transfused	27	9	18	<0·5‡

*Values are mean(s.e.m.). APACHE, Acute Physiology And Chronic Health Evaluation. †Mann–Whitney *U* test; ‡χ^2 test cavity, and the nature of the contaminant did not influence outcome. Positive blood cultures were obtained in eight patients (14 per cent) during this time, but this was not associated with an unfavourable outcome. At the time of study entry, 91 per cent of patients were receiving antibiotic therapy. In three cases the cover provided was considered to be inappropriate for the organisms typically encountered in intra-abdominal infection (one non-survivor from group 1 and two survivors from group 2). Ten alterations in antibiotic treatment were made based on microbiological findings; in six patients these alterations were considered to be inadequate (two non-survivors and two survivors from group 1, one non-survivor and one survivor from group 2). Eleven of the 33 patients who died did so as a result of progressive organ failure without apparent clinical or radiological evidence of ongoing intra-abdominal infection. At the time of death 15 patients had evidence of persistent abdominal infection (group 1, four; group 2, 11) and seven had concurrent nosocomial infections (group 1, two; group 2, five).

Acute physiology or organ failure scores and the acute phase response

The mean(s.e.m.) acute physiology score (APS) of non-survivors was greater than that of survivors at study entry (19(1·0) *versus* 15(1·0); $P = 0{\cdot}004$, Mann–Whitney *U* test) and throughout most of the study period (*Fig. 1a*). Similarly the Goris organ failure score (GOFS) was greater in non-survivors at study entry (5(0·4) *versus* 4(0·4); $P = 0{\cdot}015$, Mann–Whitney *U* test) and throughout the study period (*Fig. 1b*). When patients were stratified according to admission APACHE II score, ten of the 24 patients in group 1 had died at 30 days compared with 23 of 33 in group 2 ($\chi^2 = 5{\cdot}7$, 1 d.f., $P < 0{\cdot}025$; *Table 2*). In group 2 the APS of non-survivors was significantly higher than that of survivors in the early part of the study (*Fig. 2a* and *b*). Organ failure scores for the two groups revealed that non-survivors generally had a higher daily score during the study, the differences becoming statistically significant at day 3 in group 1 ($P < 0{\cdot}05$) and at day 2 in group 2 ($P < 0{\cdot}01$) (*Fig. 3a* and *b*).

Interleukin 6 and C-reactive protein

Mean(s.e.m.) serum IL-6 concentration at study entry was significantly higher in non-survivors (29 749(15 126) *versus* 6137(2185) pg ml^{-1}, $P = 0{\cdot}045$), as was peak IL-6 level (41 235(20 877) *versus* 6481(2155) pg ml^{-1}, $P = 0{\cdot}022$). In group 2, mean(s.e.m.) peak IL-6 concentration was significantly higher in non-survivors (55 193(28 999) *versus* 4620(2462) pg ml^{-1}, $P = 0{\cdot}03$). However, in group 1 peak IL-6 levels were not significantly different (9130(2516) *versus* 7810(3113) pg ml^{-1}, $P = 0{\cdot}22$) and the pattern of serum IL-6 concentration showed no early peak and no demonstrable differences at any time point (*Fig. 4a* and *b*). When both groups were considered together a peak IL-6 concentration greater than 4000 pg ml^{-1} was associated with an increased mortality rate (25 of 33 *versus* nine of 24; $\chi^2 = 6{\cdot}39$, 1 d.f., $P < 0{\cdot}025$). CRP profiles were similar in both group 1 and group 2, for both survivors and non-survivors (*Fig. 5a* and *b*).

Endotoxin and endogenous antiendotoxin core antibodies

At enrolment 40 patients (70 per cent) had detectable plasma endotoxin (15·8(5·9) units ml^{-1}) and during the study period 51 patients (89 per cent) had endotoxin detectable at one or more time points. Initial and peak endotoxin levels were not predictive of outcome and showed no correlation with the severity of illness as determined by either the simultaneous APACHE II score, APS or maximum daily GOFS. In group 1, IgG EndoCAb

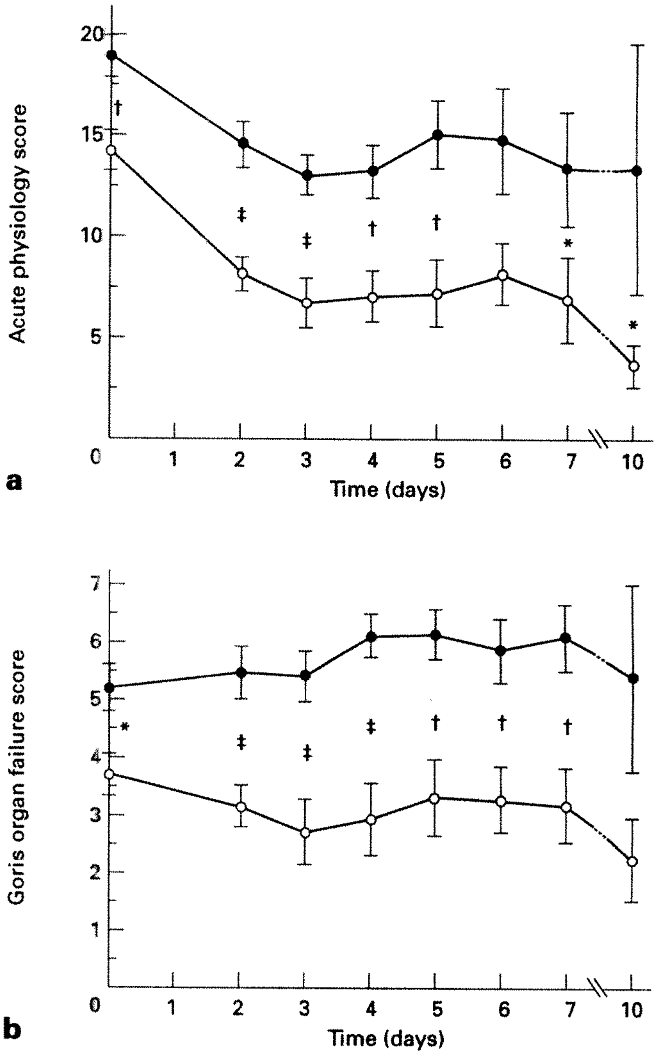

Fig. 1 Mean(s.e.m.) a acute physiology score and b Goris organ failure score for non-survivors (●) and survivors (○) over the 10-day study period. *$P < 0{\cdot}05$, †$P < 0{\cdot}01$, ‡$P < 0{\cdot}001$ (Mann–Whitney *U* test). All points indicated are also significant at the 95 per cent level for Scheffé's method for multiple comparisons

Table 2 Survival

	Day 0	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 10
Group 1 (*n* = 24)								
Survivors	14	14	14	14	14	14	14	14
Non-survivors	10	8	7	6	6	5	5	3
Group 2 (*n* = 33)								
Survivors	10	10	10	10	10	10	10	10
Non-survivors	23	15	11	11	10	9	5	4

concentration was similar in non-survivors and survivors at study entry, and tended to increase during the study period. On a day-to-day basis, this difference became significant at day 10 (*Fig. 6a*). In contrast, in group 2 overall IgG EndoCAb levels were lower in non-survivors, and on a day-to-day basis these differences were statistically significant at study entry (100·0(23·6) *versus* (216·9(50·4) GMU per ml; $P=0\cdot005$, Mann–Whitney U test) and in the latter part of the study period (*Fig. 6b*). IgG EndoCAb depletion (below the tenth centile of the value in a normal population) was observed in 12 patients (21 per cent) on entry, 11 of whom died; thus entry IgG EndoCAb depletion was associated with an increased mortality rate ($\chi^2=5\cdot47$, 1 d.f., $P<0\cdot025$). IgG EndoCAb depletion had no relationship with peak endotoxin levels (25·9(15·7) *versus* 26·5(15·3) units ml^{-1}; $P=0\cdot98$, for depleted and non-depleted). IgM EndoCAb showed a similar pattern of change (results not shown). Total IgG concentration measured at study entry was similar for non-survivors and survivors in group 1 (4·6(0·72) *versus* 4·27(0·62) units ml^{-1}, $P=0\cdot73$) and in group 2 (4·55(0·41) *versus* 4·87(0·81) units ml^{-1}, $P=0\cdot31$). There was, however, a positive correlation between IgG EndoCAb and total IgG levels measured at study entry ($r=0\cdot51$, $P<0\cdot001$, Pearson correlation).

Type 1 soluble tumour necrosis factor receptor and interleukin 1 receptor antagonist

sTNFr55 levels were higher at all three time points in non-survivors. Levels of sTNFr55 were not significantly higher in patients with detectable TNF-α compared with those in whom TNF-α was not detected (12·3(1·8) *versus* 12·5(0·9) ng ml^{-1}). Levels of sTNFr55 correlated with plasma creatinine ($r=0\cdot31$, $P=0\cdot029$). IL-1ra was present in concentrations some 2000-fold greater than those of IL-1β. IL-1ra detection was not associated with illness severity or shock at the time of study entry and was not predictive of death.

In patients with detectable IL-1β, IL-1ra was more abundant (98·6(23·8) *versus* 52·8(8·7) ng ml^{-1}, $P<0\cdot05$). IL-1ra levels were similar in non-survivors and survivors in groups 1 and 2 (46·0(13·2) *versus* 64·1(24·7) ng ml^{-1}, $P=0\cdot71$; 63·4(15·8) *versus* 47·8(14·8) ng ml^{-1}, $P=0\cdot6$).

Regression model and predictors of survival

The contribution to outcome of each variable analysed was evaluated by determining the coefficients for each in the Cox regression model. The results summarized in

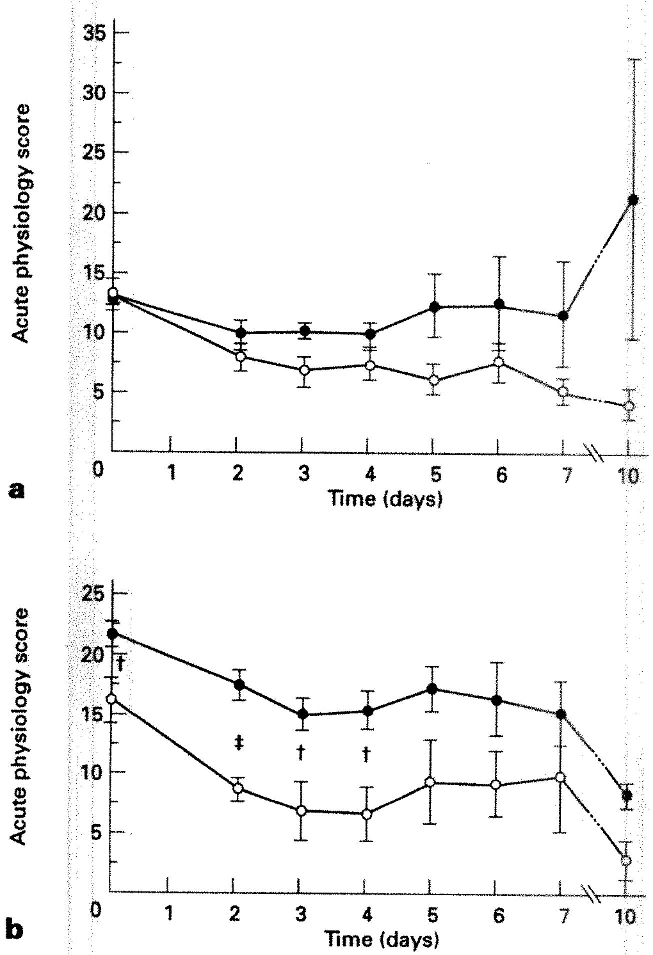

Fig. 2 Mean(s.e.m.) acute physiology score in **a** group 1 and **b** group 2 for non-survivors (●) and survivors (○) over the 10-day study period. †$P<0\cdot01$, ‡$P<0\cdot001$ (Mann–Whitney U test). All points indicated are also significant at the 95 per cent level for Scheffé's method for multiple comparisons

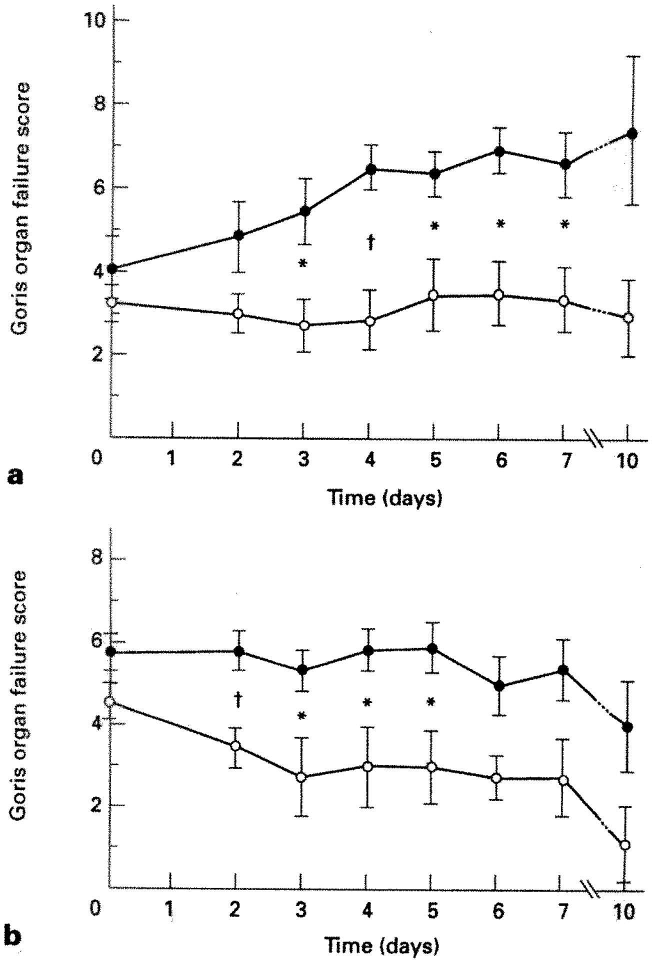

Fig. 3 Mean(s.e.m.) Goris organ failure score in **a** group 1 and **b** group 2 for non-survivors (●) and survivors (○) over the 10-day study period. *$P<0\cdot05$, †$P<0\cdot01$ (Mann–Whitney U test). All points indicated are also significant at the 95 per cent level for Scheffé's method for multiple comparisons

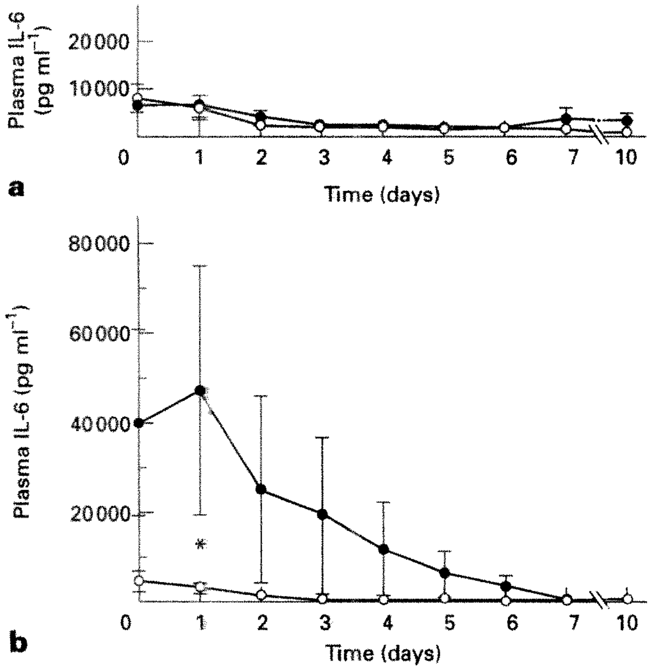

Fig. 4 Mean(s.e.m.) serum interleukin 6 levels in **a** group 1 and **b** group 2 for non-survivors (●) and survivors (○) over the 10-day study period. $^*P < 0{\cdot}05$ (Mann–Whitney *U* test), also significant at the 95 per cent level for Scheffé's method for multiple comparisons

Table 3 show that APS, GOFS and sTNFr55 level at study entry had a significant influence on outcome.

Discussion

Although the APACHE system is not specific for surgical infection, it has been advocated as the best means for risk stratification of patients with intra-abdominal infection[25]. In the present study in those with a low APACHE score (group 1), APS at study entry was identical for survivors and non-survivors, with little change over the study period. In the high APACHE score group (group 2), the initial APS of non-survivors was greater than that of survivors. A proportion of survivors was assigned to group 2 because of high scoring in the age and chronic health evaluation points. In contrast, non-survivors were entered into this group largely because of high APS. Such high APSs suggest either an overwhelming physiological insult, an exaggerated host response or a combination of the two as the main mechanism accounting for death in this group.

Clearly the trends in APS and GOFS in the present study are open to bias arising from changes in the underlying population as patients die. Indeed, in group 2 patients died more rapidly than those in group 1, and this inevitably influenced the patterns of APS and GOFS derived principally from patients who remained alive. Despite such changes in the population, both APS and GOFS act as independent predictors of outcome. Whilst it is accepted that APS is a product of the degree of physiological derangement and the level of medical intervention, it is likely to be the net physiological upset and loss of homoeostasis that is of importance.

Induction of the systemic inflammatory response by bacteria and their products has been well characterized[29–32] and the present study confirms the findings of others that endotoxin levels *per se* do not correlate with outcome. Endotoxaemia is a sporadic phenomenon[32] and measurement of endogenous antiendotoxin antibodies may be a more reliable indicator of endotoxin exposure[21]. In this series, patients with IgG EndoCAb depletion had a higher mortality rate. This depletion may reflect antibody consumption (as a result of binding to endotoxin) or in the longer term may reflect a primary failure in immunoglobulin production. In the present study on the first day of admission to the ICU, total IgG concentration was within the normal range for patients in both groups 1 and 2. This suggests that at least the initial reductions in EndoCAb levels were more related to antibody consumption than the result of non-specific mechanisms such as plasma dilution following resuscitation or a general failure of the immune system. Non-survivors in group 2 showed sustained depletion below that of survivors from either stratification group. In contrast, IgG EndoCAb levels increased progressively during the study in non-survivors from group 1. Such increasing EndoCAb levels probably reflect intermittent yet ongoing endotoxaemia, in

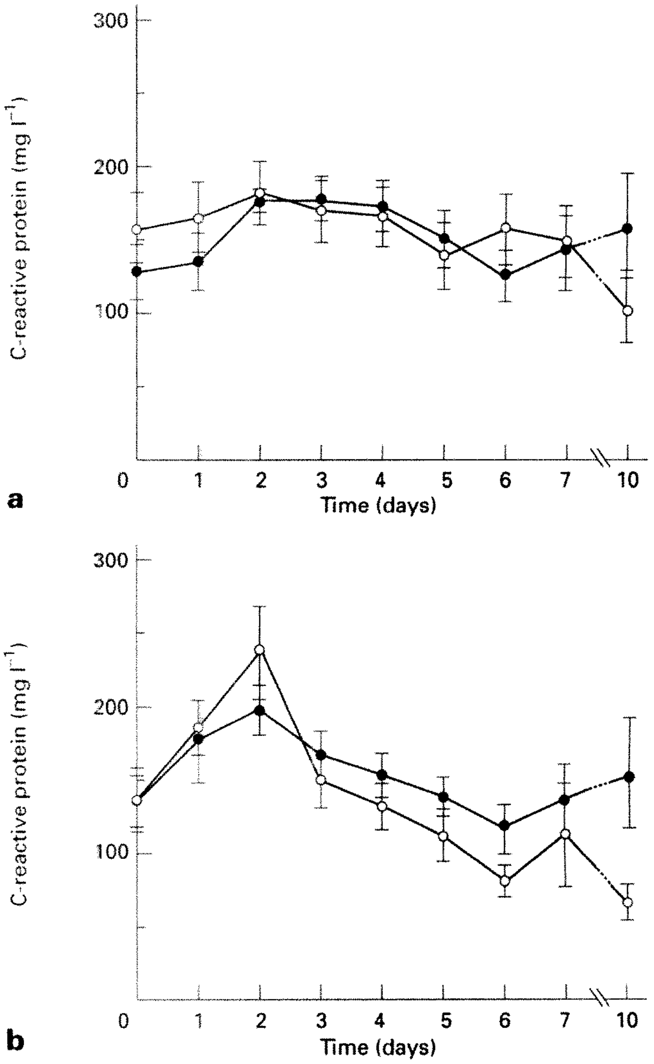

Fig. 5 Mean(s.e.m.) plasma C-reactive protein profiles in **a** group 1 and **b** group 2 for non-survivors (●) and survivors (○) over the 10-day study period

keeping with progressively rising APS and GOFS. However, unlike the patients in group 2, the initial systemic upset in group 1 is such that a normal antibody response is attainable upon initial and subsequent challenges by endotoxin. Alternatively, it is conceivable that the apparent rise in antibody titre is in part due to the death of patients who had become antibody depleted.

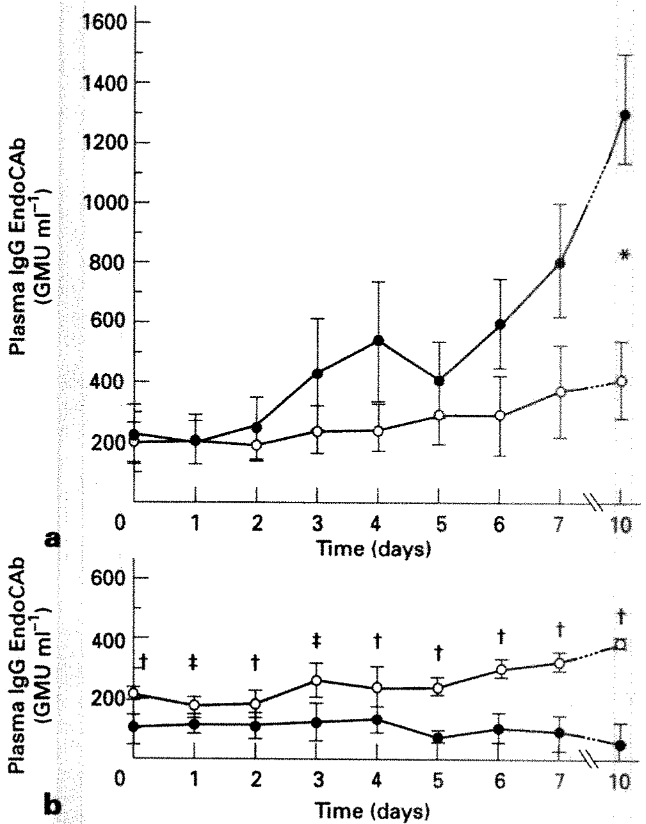

Fig. 6 Mean(s.e.m.) immunoglobulin G endogenous antiendotoxin core antibodies (IgG EndoCAb) in **a** group 1 and **b** group 2 for non-survivors (●) and survivors (○) over the 10-day study period. $^*P<0{\cdot}05$, $^\dagger P<0{\cdot}01$, $^\ddagger P<0{\cdot}001$ (Mann–Whitney *U* test). All points indicated are also significant at the 95 per cent level for Scheffé's method for multiple comparisons

It has been suggested previously that the severity of inflammation may be a key determinant of outcome in severe sepsis. In support of this, IL-6 levels have been related to the severity of tissue injury in elective surgery[33,34], and in the present study IL-6 levels were greatest in patients with the highest APS and organ failure scores. However, one of the many end-organ effects of IL-6 is the induction of hepatic acute-phase proteins such as CRP[35]. Despite the observed relationship between IL-6 levels and outcome, no detectable difference in serum CRP concentration was detected between survivors and non-survivors in either group. One explanation might be that the hepatic sites for IL-6 were saturated and circulating IL-6 levels exceeded local hepatic requirements for maximal induction of the acute-phase response. If CRP levels are taken as an index of the intensity of the inflammatory response, then the CRP profiles in the present study do not support the concept that it is the final level or duration of the inflammatory response *per se* that leads to death, as CRP levels were no different between survivors and non-survivors in either group 1 or group 2.

Non-survivors had significantly higher levels of type 1 soluble TNF receptor (sTNFr), a finding similar to that of Rogy *et al.*[36], who demonstrated that the sTNFr (representing the extracellular domain of the TNF receptor) is released in endotoxaemia. TNF exposure induces the release of sTNFr; thus the raised levels of sTNFr55 observed in non-survivors may reflect greater TNF activity or greater endotoxaemia. Furthermore, a sustained increase in the level of this antagonist is seen universally in critically ill patients, whereas in experimental endotoxaemia its presence is transitory[37]. This, of course, may not be necessarily be a reflection of a persistent systemic inflammatory response, but a failure of renal excretion of sTNFr. As in other studies[38], sTNFr55 level correlated with plasma creatinine concentration and may to some extent reflect renal impairment. The precise physiological importance of circulating cytokine antagonists such as sTNFr and IL-1ra (levels almost 2000-fold higher than those of IL-1β in the present study) remains to be elucidated. However, the failure of exogenous antagonists to improve outcome in sepsis syndrome suggests that the levels observed here may represent already replete endogenous pools.

The patients described in the present study are typical of patients in an ICU with severe sepsis from intra-abdominal infection. When stratified into risk groups by

Table 3 Cox regression analysis to evaluate the influence of individual variables on survival (results of univariate analyses)

Variable	β	SE	Wald	*P*	*R*	Exp(β)
Acute physiology score	0·0148	0·0054	7·4226	0·0064	0·1532	1·0149
C-reactive protein	− 2·39E−04 3	0·659E−04	0·4251	0·5144	0·0000	0·9998
Endotoxin	− 2·88E−04	0·0011	0·0699	0·7915	0·0000	0·9997
Goris organ failure score	0·0518	0·0187	7·6938	0·0055	0·1570	1·0532
IgG EndoCAb	− 1·20E−04 1	0·557E−04	0·5901	0·4424	0·0000	0·9999
IgM EndoCAb	− 5·96E−04 5	0·493E−04	1·1756	0·2782	0·0000	0·9994
Interleukin 6	6·462E−07	3·550E−07	3·3139	0·0687	0·0731	1·0000
sTNFr55	0·0157	0·0061	6·7184	0·0095	0·1400	1·0158
Tumour necrosis factor α	− 8·11E−04	0·0015	0·3027	0·5822	0·0000	0·9992
Interleukin 1β	− 0·0040	0·0044	0·8392	0·3596	0·0000	0·9960
Interleukin 1 receptor antagonist	− 1·39E−04 4	0·300E−04	0·1039	0·7472	0·0000	0·9999

β, beta coefficient; SE, standard error; Wald, Wald statistic; *R*, partial correlation; Exp, exponent; Ig, immunoglobulin; EndoCAb, endogenous antiendotoxin core antibody; sTNFr55, type I soluble tumour necrosis factor receptor

APACHE II score, the majority of deaths occurred in patients with an initial score of 20 or more. For the patient group overall, and specifically for those in group 2, the APS was significantly higher both at study entry and throughout the ensuing 10 days in patients who died compared with that in those who survived. It is therefore apparent that a marked systemic response to infection is associated with a poor outcome. In patients in whom the initial physiological derangement is great, there is associated increase in the levels of IL-6, depletion of antiendotoxin antibodies and raised levels of soluble TNF receptors. There remain, however, non-survivors in whom the initial physiological upset is less and in whom the pattern of response appears to be different. IL-6 profiles follow those of their surviving counterparts; antiendotoxin antibodies are replete and rise as in a normal immune response. The mechanism of death in these patients is less clear and is worthy of further study.

If the initial systemic inflammatory response and ensuing organ dysfunction are a main influence on outcome, their development may be conditioned at several levels: first, at the level of induction of proinflammatory mediators by bacteria and their products; second, at the level of transcription of these mediators; and third, at the level of the effector cell and end-organ. Correct surgical practice should limit the bacterial inoculum, minimizing the induction process. With regard to host mediator responses (which may be predetermined genetically[39]), it is apparent that mediator and antagonist activity can differ markedly and their measurement in isolation cannot predict prognosis. The window of opportunity in modulating proinflammatory events is small and the exact requirements are difficult to define. However, early identification of idiosyncrasies in patient responsiveness and damage limitation at end-organ sites are avenues that should be explored further.

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Experimental study of adhesion formation in open and laparoscopic fundoplication

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Background The extent of adhesion formation following both open and laparoscopic surgery remains unclear. This study aimed to evaluate the extent of postoperative adhesion formation after laparoscopic and open fundoplication in a rat model.

Methods Fifty-two male Sprague–Dawley rats were randomized into four groups: laparoscopic fundoplication ($n = 20$), open fundoplication ($n = 20$), laparoscopy ($n = 6$) and laparotomy ($n = 6$). Blood as well as intraperitoneal fluid was sampled for tumour necrosis factor (TNF) α measurement by enzyme-linked immunosorbent assay. All the rats were killed 3 weeks after operation, and adhesion formation was evaluated using a standardized scoring system.

Results There were no intergroup differences in body-weight gain after surgery. The overall mortality rate was 19 per cent and death was observed only in the fundoplication groups. Animals that had open fundoplication developed significantly more adhesions than those that underwent laparoscopic fundoplication (34 *versus* 21). Laparoscopic surgery induced predominantly parietal adhesions, whereas open surgery was more associated with visceral adhesions. The adhesions observed in the laparoscopic groups were significant thinner than those after open surgery and the tenacity of adhesions was decreased in laparoscopic compared with open surgery. The peak plasma level of TNF-α was reached during laparoscopic fundoplication, whereas the peak level was observed 3 h after open fundoplication. Intraperitoneal TNF-α levels showed no significant differences at 3 h.

Conclusion These findings indicate that laparoscopic fundoplication in rats leads to less severe adhesions of a different type (parietal) compared with those seen in the open controls.

The increasing use of minimally invasive surgery has played an important role in the development of abdominal surgery at the end of the 20th century. Along with the wider application of minimally invasive surgical procedures[1-3], there is a growing interest in the physiological changes that occur compared with those during open surgery[4-9]. Open surgical procedures may cause postoperative adhesion formation, leading to delayed postoperative complications such as abdominal pain[10,11], infertility[12,13] and bowel obstruction[14-16]. There are few fundamental scientific data available in the literature concerning the pathophysiological changes (local and systemic) that occur during laparoscopic surgery[17].

The development of laparoscopic surgery was based on experimental animal research. The use of large animals, such as pigs or dogs, in surgical research is also associated with increased costs[4,18]. The rat model has been shown to be an excellent training model for performing microsurgical procedures[4,19], providing the opportunity to investigate physiological changes, adhesion formation and immune function during different laparoscopic procedures. Several studies suggested that tumour necrosis factor (TNF) α, an acute-phase cytokine, may be one of the markers of peritoneal adhesion formation[17,20-22]. The purpose of this study was to develop a standardized laparoscopic procedure (i.e. Nissen fundoplication) in the Sprague–Dawley rat model and to compare it with an open approach to investigate and correlate adhesion formation and TNF-α production during and after surgery.

Materials and methods

Animals and study design

The experiments were approved by the Animal Ethics Committee of the State of Berne and performed according to international guidelines. Fifty-two male Sprague–Dawley rats, weighing 300–460 g (Süddeutsche Versuchstierfarm, Tuttlingen, Germany), were used for all the experiments. They were kept under normal laboratory conditions and were fed a standard rat chow (Kliba Futter, Basel, Switzerland) with tap water *ad libitum* before and after surgery. The rats were divided into four main groups. Groups 1 ($n = 20$) and 2 ($n = 20$) underwent laparoscopic or open fundoplication respectively and determination of TNF-α levels in plasma and peritoneal fluid following surgery. Group 3 ($n = 6$) underwent diagnostic laparotomy and group 4 ($n = 6$) diagnostic laparoscopy.

Blood and peritoneal fluid sampling for tumour necrosis factor analysis

Venous blood was sampled from the external jugular vein of all the animals on induction of anaesthesia, during the operation and 1, 3 and 24 h after operation, and collected into 5·5-ml Monovette AH (Nümbrecht, Sarstedt, Germany) tubes containing ammonium-heparin (15 units heparin per ml blood). Plasma was obtained by centrifugation for 10 min at 2500g and 4°C, collected into 1·5-ml plastic snap-cap tubes and stored at −20°C until analysis. Peritoneal fluid was obtained 3 h after surgery by vacuum absorption from the peritoneal cavity through a polythene tube (catheter) 0·58 mm in diameter and 4–5 cm

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long, which was inserted at the end of the open and laparoscopic procedure and stored at −20°C until analysis. The Cytoscreen Rat TNF-α kit (Cannon, Labor Service GMBH, Wiessbaden, Germany) was used for the TNF-α analysis.

Surgical procedures

All the animals used in the study were anaesthetized by intraperitoneal injection of a mixture (1 ml per kg body-weight) of 25 ml 5 per cent glucose, 5 ml azepromazin, 5 ml xylazin and 10 ml ketamin. The animals were shaved and secured in a supine position to the small-animal operating table[4]. The instruments used for all the laparoscopic procedures were a 2·7-mm arthroscope with a 3-mm trocar sleeve, two 3-mm trocars (working channels) and 2·7-mm instruments (scissors, straight and angled forceps, needle holder; Wolf, Tuttlingen, Germany). Ordinary small-sized hand surgery instruments were used for all open procedures. All procedures were performed without using swabs or wearing gloves. In the open procedure the abdominal wall was retracted with two sutures, so iatrogenic manipulation at this side was minimal.

Laparoscopy was performed through a 3-mm abdominal wall incision, midway as described by Berguer *et al.*[4]. Pneumoperitoneum was established with carbon dioxide insufflation up to 4 mmHg (abdominal pressure). Diagnostic laparoscopy (no procedure performed) lasted 30 min, after which all the trocar sleeves were removed and the wound closed with two single stitches. Laparoscopic fundoplication started with blunt dissection of the adhesions between the caudate liver lobe and the lesser curvature. The oesophagus, left gastric artery and anterior vagus nerve were identified and the oesophagus grasped and retracted anteriorly. Following this, an opening behind the oesophagus was created bluntly. The fundus of the stomach was grasped through the opening, pulled behind the oesophagus, turned ventrally and sutured extracorporeally with two 5/0 Vicryl sutures (Ethicon, Spreitenbach, Switzerland). A polythene tube 0·58 mm in diameter and 4–5 cm long was inserted through the left sleeve to the abdominal cavity for peritoneal fluid collection. The pneumoperitoneum was desufflated through the camera port and all the trocars were removed in order to prevent initial tissue attachments to the port sites.

All open procedures were performed using the same technique via a standardized 3-cm midline incision. Diagnostic laparotomy also lasted 30 min. Open fundoplication was performed with two 5/0 Vicryl single stitches. Before closure, a polythene catheter was inserted into the abdominal cavity for peritoneal fluid collection. The laparotomy was closed with a 3/0 Vicryl running suture in two layers.

Postoperative observation and determination of adhesion formation

The animals were observed in single cages for 24 h after operation until all the necessary blood and peritoneal fluid samples had been taken. After that, they were kept and observed under standard laboratory conditions. Three weeks after operation the animals were killed by decapitation and the abdominal cavity was opened by a wide inverted U-shaped laparotomy to investigate the extent and type of adhesion formation by two independent surgeons. The special criteria of Egea Moreno *et al.*[23], as shown in *Table 1*, were used to determine the extent of adhesions, as well as their localization, thickness, tenacity and vascularization.

Statistical analysis

Means were compared with an unpaired *t* test. $P < 0{\cdot}05$ was considered to be statistically significant.

Results

Operating time, body-weight, follow-up and death

The operating time ranged from 15 to 45 (mean 28) min for laparoscopic fundoplication and from 15 to 37 (mean 25) min for open fundoplication. All animals had a normal, proportional body-weight gain at 1, 2 and 3 weeks following surgery and there were no significant differences (data not shown). The overall mortality rate was 19 per cent and deaths occurred only in the two fundoplication groups (five deaths in each). Early death (from anaesthesia, bleeding, pneumoperitoneum) occurred in six animals and delayed death (due to septic complications) in four.

Table 1 Quantification of adhesion formation

Criterion	Comment
No. of adhesions	1 for each
Site of adhesions	
Pelvic fat body–abdominal wall	Parietal
Omentum–abdominal wall	Parietal
Intestine–abdominal wall	Parietal
Omentum–liver/stomach	Visceral
Intestine–intestine	Visceral
Liver–stomach	Visceral
Thickness of adhesions	
< 3 mm	
3–5 mm	
> 5 mm	
Tenacity	
Type I	Simple, without dissection
Type II	Dissection needed to separate adherent area
Type III	Dissection needed to cut the adhesion
Vascularization of adhesions	
Vascularized	
Avascularized	

Total adhesion score is the sum of each criterion (site of adhesions, thickness, tenacity and vascularization)

Adhesion formation

Number of adhesions. Five animals that underwent laparoscopic fundoplication, two that had diagnostic laparoscopy and two that had diagnostic laparotomy still had not developed adhesions 3 weeks after surgery, whereas adhesions were detected in all animals that had open fundoplication (*Table 2*). The 15 animals that had

Table 2 Adhesion formation after laparoscopic or open Nissen fundoplication

	Laparoscopic fundoplication ($n = 15$)	Open fundoplication ($n = 15$)
Animals with adhesions	10	15
No. of adhesions	21	34
Site of adhesions		
Parietal adhesions	13	5
Visceral adhesions	8	29
Intestine involved (bowel, stomach, liver)	11	30
Thickness of adhesions		
< 3 mm	12	3
> 3 mm	9	31
Tenacity		
Type I + II	12	6
Type III	9	28

There were no differences in vascularization between the groups laparoscopic fundoplication developed 21 adhesions, whereas 34 adhesions were detected in the 15 animals that underwent open fundoplication. Rats that had diagnostic laparoscopy and laparotomy ($n = 6$ each) developed five and six adhesions respectively. The number of adhesions differed significantly ($P < 0{\cdot}05$) between laparoscopic and open fundoplication groups. No significant differences were observed in comparison with the other groups.

Site of adhesions. Animals that had laparoscopic surgery (laparoscopic fundoplication and diagnostic laparoscopy) developed predominantly parietal adhesions (13 of 21 after laparoscopic fundoplication and all five after diagnostic laparoscopy), mostly between the small intestine (three) or omentum (ten) and the scars of the optical or working trocars of the abdominal wall. There was no predominance of adhesion formation between the optic and working trocars. Animals that only underwent laparotomy also developed more parietal adhesions (five of six) between the small bowel or the omentum and the laparotomy scar. Conversely, animals that underwent open fundoplication developed predominantly visceral-type adhesions (29 of 34), especially between the intestine (two), liver/stomach and omentum (six) as well as between the stomach and liver (21). The distribution of adhesions after open fundoplication was significantly different from that after laparoscopic fundoplication ($P < 0{\cdot}01$) and diagnostic laparoscopy and laparotomy ($P < 0{\cdot}01$). No significant difference was seen between diagnostic laparoscopy and laparotomy. There was no significant difference in the distribution of visceral adhesions after laparoscopic fundoplication (six liver and stomach, three liver/stomach and omentum) and open fundoplication (23 and six respectively). However, a significant difference in adhesion formation involving intestine (liver, stomach, bowel) between laparoscopic fundoplication (11 of 21) and open fundoplication (30 of 34) was found ($P < 0{\cdot}05$).

Thickness of adhesions. The thickness of adhesions after laparoscopic and open fundoplication was significantly different ($P < 0{\cdot}05$) and inversely proportional. Animals that had laparoscopic surgery (laparoscopic fundoplication and diagnostic laparoscopy) mostly developed adhesions less than 3 mm thick (12 of 21 and three of five respectively), whereas those that had open surgery (open fundoplication and diagnostic laparotomy) mostly developed adhesions more than 5 mm thick (*Table 2*).

Tenacity. Animals that had a laparoscopic intervention mostly developed type I and II adhesions (12 of 21 after laparoscopic fundoplication and all five after diagnostic laparoscopy respectively), whereas open surgery was followed mainly by the development of type III adhesions (28 of 34 after fundoplication and four of six after diagnostic laparotomy) (*Table 2*). A small number of type I adhesions was noticed in all groups. Only type II adhesions developed after diagnostic laparoscopy. There were significant differences between open and laparoscopic surgery (laparoscopic *versus* open fundoplication, $P < 0{\cdot}01$; open fundoplication *versus* diagnostic laparoscopy, $P < 0{\cdot}05$).

Vascularization of adhesions. All animals primarily developed vascularized adhesions. However, after laparoscopic and open fundoplication one-fifth and one-quarter of the adhesions respectively were avascularized. All the adhesions that developed after diagnostic laparoscopy were vascularized, whereas half of those that developed after diagnostic laparotomy were avascularized. There were no significant differences between all the groups investigated. Overall adhesion score[23] is summarized in *Fig. 1*.

Tumour necrosis factor concentrations

There were different TNF-α ranges in the fundoplication groups (*Fig. 2*). Laparoscopic fundoplication induced an early intraoperative peak of TNF-α secretion in plasma and the preoperative level was reached 24 h after surgery. Open fundoplication induced only a slight rise in TNF-α secretion at operation and 1 h after operation; the peak

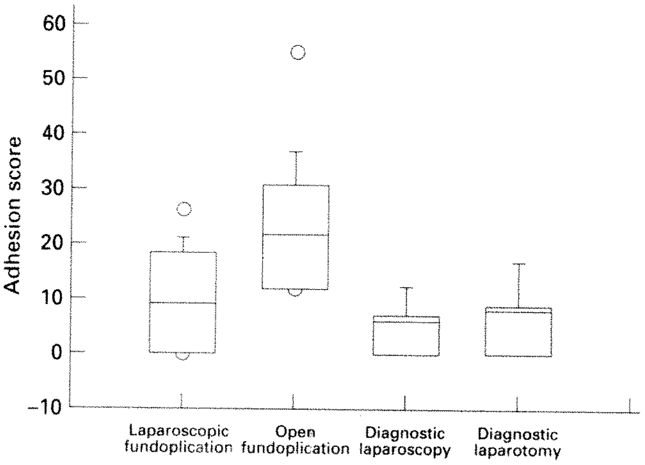

Fig. 1 Total adhesion scores in the four surgical groups. Boxes include values between the 5th and 95th percentile with the median values (horizontal line). T bars indicate standard deviations. Values outside the standard deviation are indicated as open circles. The adhesion score was significantly higher after open fundoplication than after the other procedures ($P < 0{\cdot}01$, unpaired t test)

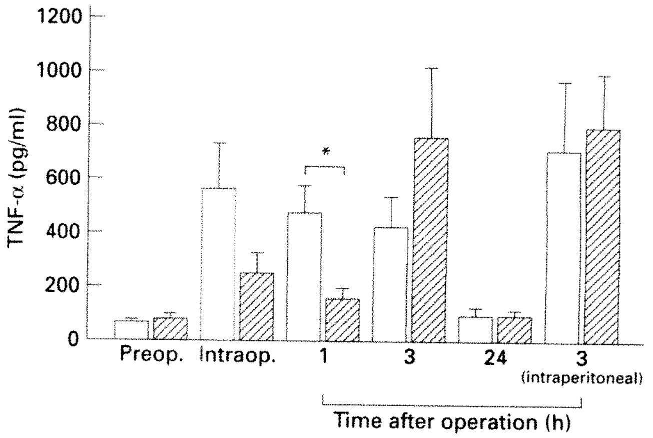

Fig. 2 Plasma and intraperitoneal tumour necrosis factor (TNF) α levels following laparoscopic (□) or open (▨) fundoplication. Values are mean(s.e.m.) $^{*}P < 0{\cdot}05$, unpaired t test

TNF-α level occurred 3 h after operation. Some 24 h after surgery, the TNF-α level had again reached preoperative levels. TNF-α secretion was significantly different between laparoscopic and open fundoplication groups ($P < 0{\cdot}05$) 1 h after surgery, whereas all other plasma TNF-α values for the two fundoplication groups showed no significant differences. TNF-α concentrations, measured 3 h after operation in the peritoneal fluid, were increased after open fundoplication compared with laparoscopic fundoplication (*P* not significant). Comparison of peritoneal TNF-α concentrations with adhesion tenacity showed that no adhesions developed with TNF-α levels of 200 pg/ml or less.

Discussion

The present study demonstrates that laparoscopic and open Nissen fundoplication are technically feasible in the rat model and that a different extent (more after open surgery) and type of adhesion formation between laparoscopic fundoplication (parietal) and open fundoplication (visceral) are induced.

The development of peritoneal adhesions is an inevitable outcome of surgical operations in the abdominal cavity. It is one of the main complications, occurring some weeks or months after the initial operation[17], and it results in morbidity following abdominal, gynaecological, or cardiac surgical procedures. Such complications are visceral dysfunction, chronic abdominal pain, infertility and early or delayed bowel obstruction[10,14,15,23]. Morbidity due to adhesion formation is associated with increased socioeconomic costs, which reach up to $1.18 million in the USA per year[12]. Menzies and Ellis[14] published a prospective trial of 210 patients with a history of previous abdominal surgery who underwent a 'second-time' laparotomy; peritoneal adhesions were found in 93 per cent. Furthermore, in 115 patients who underwent first-time laparotomy, abdominal adhesions were demonstrated in 10 per cent.

Multiple factors may be responsible for the development of postoperative adhesions, for example the extent of surgical trauma and length of the procedure, bacterial contamination, allergic reactions to inserted foreign bodies and tissue ischaemia[17]. All of these factors cause peritoneal tissue injury, which leads to an inflammatory reaction and cytokine release, which are considered to be trigger mechanisms for further adhesion development. Thus, mesothelial, inflammatory and endothelial cells are activated to produce and release plasminogen activator inhibitors 1 and 2, which predispose to the loss of plasminogen activation in the injured area of the peritoneum. This process leads to impairment of fibrinolysis, fibrin coagulation and fibrin matrix formation[17,24,25].

Kaidi *et al.*[20,21] found a direct correlation between the grade of injury, TNF-α secretion and the extent of peritoneal adhesion formation. In the present series, during laparoscopic fundoplication there was a rapid rise in plasma TNF-α level, reaching its peak at operation and gradually decreasing to preoperative levels by 24 h after surgery. In contrast, there was only a slight TNF-α rise during and 1 h after open surgery, with a peak level 3 h after surgery. Again 24 h after surgery TNF-α levels were the same as those before operation. The overall TNF-α concentrations in the peritoneal fluid were higher than those in plasma 3 h after surgery and were slightly increased following open surgery (*P* not significant). These findings suggest that TNF-α may be produced primarily in the peritoneal cavity, secreted into the operative field and afterwards absorbed into the systemic circulation. This means that the TNF-α produced during the open procedure may well have been lost externally (open cavity, rinsing), and this may explain the fact that TNF-α levels were reduced during open fundoplication and 1 h afterwards. It also explains why no correlation between TNF-α levels and tenacity of adhesion formation was found and that any assessment of TNF as a measure of inflammatory response in the peritoneum may be inappropriate. A similar tendency was observed in other series which investigated the inflammatory cytokine response following abdominal surgical procedures[22].

No adhesions were detected in the abdominal cavity following intraperitoneal anaesthesia and skin incision, which suggests that surgical trauma alone without opening the peritoneal cavity is not responsible for adhesion development ($n = 7$; data not shown). A minimal surgical trauma, such as diagnostic laparoscopy or diagnostic laparotomy without further surgical intervention or bowel revision, leads to less adhesion formation than upper gastrointestinal surgery. Laparoscopic Nissen fundoplication leads to less postoperative adhesion formation than the open procedure. Furthermore, adhesions in the laparoscopic group were of the parietal type, from omentum or small bowel to the parietal peritoneum, rather than the visceral type, developed between the abdominal organs themselves.

Similar observations were published by Tittel *et al.*[26] in a canine model, and by Semm[27] in humans. Semm clearly demonstrated in women who underwent diagnostic laparoscopy after previous abdominal operations (open or laparoscopic) that 84 per cent had adhesion formation after open surgery whereas only 40 per cent did after laparoscopic intervention. However, in his series it remained unclear which type of adhesions was responsible for the development of postoperative complications.

In conclusion, the present study demonstrates that laparoscopic surgery is technically feasible in the rat model with low morbidity and mortality rates at long-term follow-up. Postoperative adhesion formation occurred more frequently and severely after open surgery compared with the same operation performed laparoscopically. The TNF-α levels measured intraperitoneally did not differ between the two groups, and a positive correlation between the tenacity of adhesion formation and the intraperitoneal TNF-α level was not found. This animal model can be used for laparoscopic surgery and the study of adhesion formation. However, further studies are needed to evaluate the pathophysiological changes leading to postoperative adhesion formation and its prevention.

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Ignoring small lymph nodes can be a major cause of staging error in gastric cancer

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Background Stage migration in gastric cancer confounds establishment of standard treatment according to stage.

Methods To determine how closely lymph nodes should be examined to report correct staging, 402 node-positive patients were evaluated retrospectively. A total of 23 233 lymph nodes were reviewed histologically and their maximum dimension was measured. Another 254 nodes from 12 patients were used to evaluate shrinkage after fixation and preparation of the histological slide.

Results Metastasis was detected in 3142 nodes, 1163 with well differentiated tumours (WDTs) and 1979 with poorly differentiated tumours (PDTs). Mean(s.d.) size of metastatic nodes was 7·80(5·08) mm in all, 8·44(5·74) mm in WDTs and 7·42(4·62) mm in PDTs. Both positive and negative nodes shrank between 10 and 20 per cent during histological processing. If all nodes 5 mm or less in size when fixed are ignored 37·8 per cent of all metastatic nodes will be missed. Downstaging will occur in 14·9 per cent and 4·2 per cent of the cases if all nodes less than 6 and 4 mm respectively are ignored.

Conclusion To keep the rate of stage migration caused by this factor below 5 per cent, all lymph nodes 4 mm or more in size (5 mm when fresh) should be retrieved and examined.

In the treatment of malignant disease, the selection of primary or adjuvant treatment is often decided by stage. Evaluation of new treatments and comparison of outcomes in different countries are possible only if a common stage system is properly applied. In most solid tumours, the tumour node metastasis (TNM) classification of the Union Internacional Contra la Cancrum (UICC) is the most commonly used classification. Because the pTNM closely correlates with prognosis, it is often included in clinical trial protocols. Stage migration can occur easily in any category of TNM[2], especially in N or pN stage, for several reasons including more extended nodal dissection, retrieving more nodes from the specimen or more sectioning of each node[3]. Stage migration caused by extended surgery has been discussed extensively[4], but the other two factors have not yet been well evaluated for gastric cancer, although clinical practice among pathologists varies enormously from country to country. In Japan lymph nodes are retrieved from the fresh *en bloc* specimen by surgeons and as many nodes as possible are examined by pathologists. In many western countries, it is the pathologists who retrieve nodes and examine them. The number examined per specimen varies between countries and between pathologists[5]. Among the various factors influencing lymph node retrieval, this study focused on the size, as this seems to be one of the most important factors and other factors are difficult to assess objectively. To minimize stage migration it is important to know how many nodes should be examined and whether small nodes can be ignored. In this study, the relationship between metastatic state and nodal size was studied to determine the impact of ignoring small nodes on stage migration in patients with gastric cancer.

Patients and methods

A total of 1741 patients underwent gastric resection for gastric carcinoma between 1986 and 1991. Some 427 patients treated with curative intent were node positive, of which 402 were included in this study, while 25 were excluded because of insufficient data.

Immediately following D_2 (level 1 and 2 lymphadenectomy) or more extended gastrectomy all lymph nodes that were detectable by sight and palpation and attached to the resected specimen were retrieved by surgeons. Lymph nodes were divided into groups by their station according to the Japanese Classification of Gastric Carcinoma[6]. They were fixed in 10 per cent formalin solution and processed for pathological investigation. Lymph nodes were cut in two through the hilum along the long axis and embedded in paraffin. Nodes of 3 mm or less were embedded in paraffin whole. Sections measuring 3 μm in thickness were obtained from each paraffin block and stained with haematoxylin and eosin. This procedure is known to cause a reduction in the size of lymph nodes. The reduction rate was calculated by measuring a further 254 lymph nodes from 12 patients before and after the procedure.

All lymph nodes were examined for metastases and the size of each lymph node was measured on the glass slide. Metastatic lymph nodes were also divided into two groups by the level of differentiation of the primary tumour: WDT included well and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma, and PDT included poorly differentiated adenocarcinoma, signet-ring cell carcinoma and mucinous adenocarcinoma. The size of lymph nodes was evaluated in relation to metastatic state and the histological type of the primary tumour.

Lymph node data, i.e. location, size, metastatic state and histological type, were recorded for every lymph node of each patient and the pN stage was determined according to the Japanese Classification of Gastric Carcinoma[6]. Downstaging that would be

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caused by ignoring all nodes smaller than a certain size was calculated.

Statistical analysis of shrinkage rate and lymph node size were carried out using Wilcoxon's rank sum score test; other analyses on the 23 233 nodes were performed using analysis of variance.

Results

Shrinkage rate

Of 254 lymph nodes, 25 were metastatic and the rest were non-metastatic. The mean relative size after the process of preparing glass slides was 0·84 (fresh size 1·0) and the shrinkage rate was thus 16 per cent. There was no significant difference in shrinkage rate between metastatic and non-metastatic lymph nodes at any size (*Table 1*). The shrinkage rate was smallest with nodes of 5 mm or less and greatest between 6 and 10 mm, irrespective of metastatic state.

Size of lymph node and stage migration

A total of 23 233 lymph nodes in 402 patients were examined. The mean number of retrieved nodes was 57·8 per resected specimen. Mean(s.d.) size was 5·64(3·40) mm. Modal size of the lymph nodes was 3 mm (14·9 per cent) and 63·8 per cent of all lymph nodes ranged from 2 to 6 mm.

Mean(s.d.) size of the metastatic lymph nodes was 7·80(5·08) mm, while that of non-metastatic nodes was 5·30(3·05) mm ($P < 0{\cdot}0001$) (*Fig. 1*). If all lymph nodes less than 5 mm in size had been ignored, 26·4 per cent of all metastatic nodes would have been missed. Similarly 37·8 and 73·0 per cent of involved nodes would have been missed if nodes smaller than 6 and 10 mm respectively had been ignored.

Among the metastatic lymph nodes, a significant difference in the mean size was seen between the WDT and PDT groups (*Table 2*).

Table 1 Mean(s.d.) relative size of lymph nodes after fixation and preparation of glass slides (size in fresh state 1·0)

Size (mm)	Metastatic lymph nodes	Non-metastatic lymph nodes	Total
5 or less	0·91(0·12) (5)	0·89(0·17)† (87)	0·89(0·17)‡ (92)
6–10	0·78(0·11)* (11)	0·81(0·11) (98)	0·80(0·11) (109)
Over 10	0·87(0·11) (9)	0·82(0·11) (44)	0·83(0·11) (53)

Values in parentheses after mean(s.d.) are number of nodes examined. $^{*}P < 0{\cdot}05$ *versus* metastatic nodes of other size; $^{\dagger}P < 0{\cdot}001$ *versus* metastasis-free nodes of other size; $^{\ddagger}P < 0{\cdot}001$ *versus* nodes of other size, Student's t test

Table 2 Size of metastatic lymph nodes and histology of primary tumour

Histology of primary tumour	No. of cases	No. of lymph nodes	Mean(s.d.) size (mm)
WDT	179	1163	8·44(5·74)
PDT	223	1979	7·42(4·62)*
Total	402	3142	7·80(5·08)

WDT, well differentiated tumour; PDT, poorly differentiated tumour. $^{*}P < 0{\cdot}0001$, Student's t test

Table 3 Incidence of stage migration by ignoring small nodes

	Size of lymph node ignored (mm)				
	1–2	1–3	1–4	1–5	1–9
Stage migration (n)	6 (1·5)	17 (4·2)	31 (7·7)	60 (14·9)	167 (41·5)
Shift to pN_0 (n)	5 (1·2)	15 (3·7)	25 (6·2)	48 (11·9)	112 (27·9)

Values in parentheses are percentages

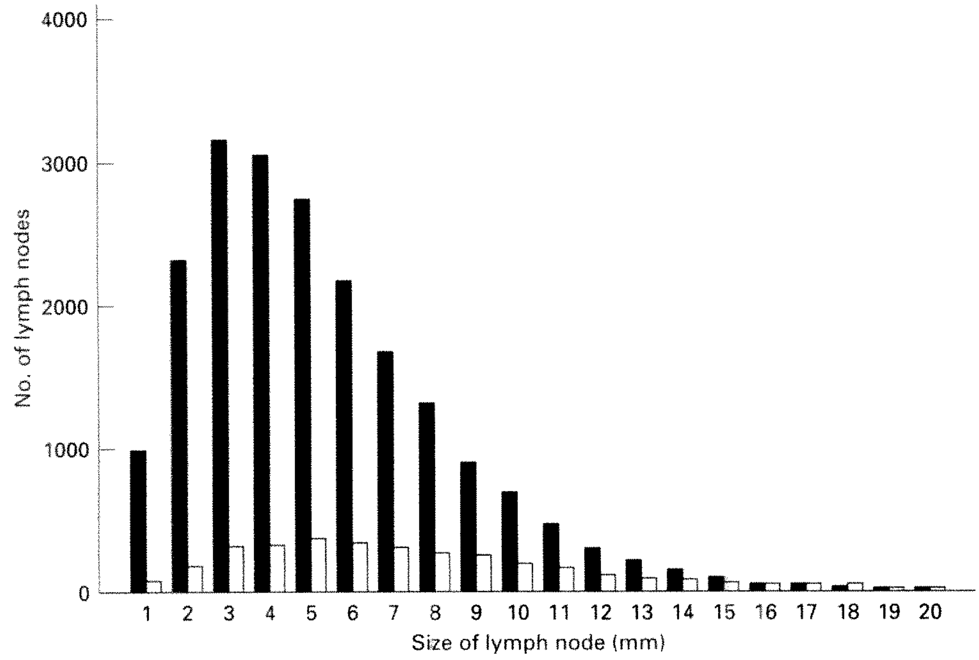

Fig. 1 Size distribution of metastatic (□) and non-metastatic (■) lymph nodes

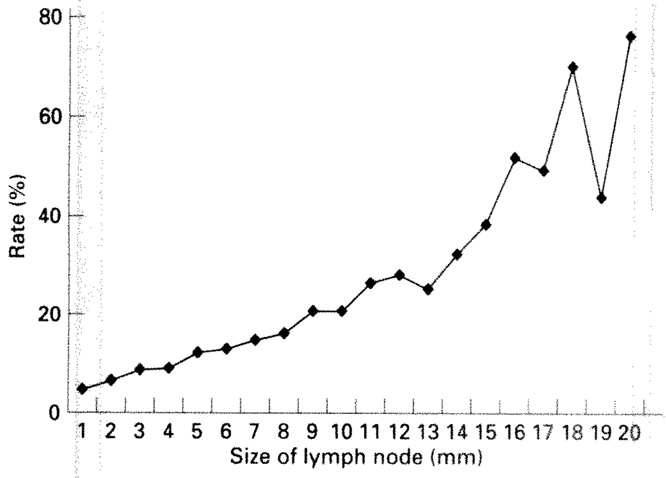

Fig. 2 Rate of metastatic nodes according to the size of lymph nodes

The proportion of positive nodes increased with the size of lymph nodes (*Fig. 2*). Only 5 per cent of 1-mm lymph nodes were metastatic, whereas 12 per cent of 5-mm and 21 per cent of 10-mm nodes had metastases.

The number of patients who would be downstaged if small nodes were ignored was calculated, as was the percentage of cases in which downstaging to pN_0 occurred (*Table 3*).

Discussion

TNM classification is not simply an instrument to assist in the prognosis, it also provides essential information on the basis of which the physician can plan treatment. Hammond and Henson[7] emphasized the important role of pathologists in the management of patients with cancer. Several methods have been described for obtaining accurate staging of lymphatic spread; some aimed at better retrieval of nodes and others at better detection of the microfoci of metastasis. The fat clearance method resulted in 7 per cent upstaging in 41 patients with colorectal cancer[8], and 29 per cent upstaging in 11 patients with gastric cancer[9]. It certainly provides more accurate pN stage information but is too labour-intensive for routine use in clinical practice. Serial sectioning and immunostaining are possible methods for detecting micrometastases but it is impracticable to carry out complete serial sectioning of all lymph nodes. In a theoretical evaluation Wilkinson and Hause[10] predicted a detection rate of 0·5 mm foci in 5-mm nodes of 16 per cent by a single central section but up to about 40 per cent by using three sections, the central and two quarter sections, with the assumption that each node contains only one micrometastatic focus. When Natsugoe *et al.*[11] compared making four sections from each node with the conventional one section method, only four of 304 nodes in patients with gastric cancer had micrometastatic foci that were not detected by the conventional method. More than one-half of these microfoci were less than a maximum of 0·5 mm in dimension. The theoretical evaluation of Wilkinson and Hause[10] does not, therefore, reflect reality, and any realistic practical method of node examination seems unlikely to have an impact on stage migration.

Several authors have reported the usefulness of immunostaining using antibodies to keratin or carcinoembryonic antigen for colorectal carcinomas[8,12,13]. According to these authors, about 5 per cent more metastatic nodes were found and stage shift occurred in about 30 per cent of patients with colorectal carcinoma. Recently, Siewert *et al.*[14] reported a high detection rate (90 per cent) of individual cancer cells in patients with pN_0 by using antibodies to human cytokeratins, but the clinical implication and prognostic significance of these 'individual tumour cells' detected in lymph nodes are still uncertain. Such cancer cells are nominated as 'micro involvement' to distinguish them from 'micrometastasis' which is defined as a tumour nest having a stromal reaction. Routine use of these methods would double or triple the workload of preparing slides because double staining is not acceptable. Recently Hayashi *et al.*[15] reported the efficacy of genetic diagnosis of lymph node metastasis in colorectal cancer. This method can detect micrometastasis at the level of an individual cell, but is available only for tumours that have a genetic mutation suitable for polymerase chain reaction detection. Because of the lower rate of specific gene abnormality in gastric cancer and greater genetic heterogeneity than in colorectal cancer, this technique seems to be of little value for gastric cancer at present[16,17].

The methods that increase the detection rate of micrometastasis can be effective only when reasonable numbers of nodes are retrieved. Retrieving small nodes does not require any special technique, but diligence and time. It may be more difficult to retrieve sufficient numbers of small nodes from western patients, who generally have higher levels of body fat than Japanese, but from personal experience (M.S.) it is possible to retrieve an average of 60 nodes per specimen, which is equivalent to the number reported in this paper[18].

The mean size of metastatic nodes of WDT is significantly larger than that of PDT, but more than one-third of metastatic nodes in the former are smaller than 6 mm. Therefore the principles of retrieval should be applied irrespective of histological type of primary tumour.

Although retrieving many small apparently normal nodes is laborious, it remains much more feasible than the fat clearance method. Moreover, Bunt *et al.*[18] have suggested that retrieving from a fresh specimen might be more accurate than the fat clearance method if performed by an experienced surgeon, and that it can be as good as the fat clearance method if done by ordinary pathologists. The present data showed that 37·8 per cent of metastatic nodes were 5 mm or less in diameter. At this size, the shrinkage rate is about 10 per cent and the size evaluated on the glass slides is almost the same as that in the fresh state. If all of these nodes are ignored, stage migration will occur in 14·9 per cent of cases, among which 11·9 per cent will be downstaged to pN_0. In one study[9], the mean number of retrieved nodes using conventional methods was only 17·7 per specimen, which is 18·5 smaller than the mean number yielded by the fat clearance method. In the Dutch Gastric Cancer Trial[18] it was reported that the number of retrieved nodes was ten or fewer in 43 of 113 cases (38 per cent) treated by limited surgery and 20 or fewer in 43 of 114 (38 per cent) treated by D_2 gastrectomy. Ten or 20 is a much smaller number of lymph nodes than the expected average from a gastrectomy specimen of respective type[18]. The lack of diligence implied by these figures reflects the generally poor understanding of the impact of ignoring small nodes on stage migration. The best surgical treatment and adjuvant therapy for gastric cancer is still the subject of clinical trials[19,20]. Failure to establish the gold standard is partly a result of a lack of stratification by stage in these trials. Pathologists should be fully aware of the importance of exact staging and their role in establishing the stage specific treatment of choice.

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Lymph node metastasis of early gastric cancer with submucosal invasion

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Background A clinicopathological study of early gastric cancer with submucosal invasion was carried out in relation to lymph node metastasis.

Methods A retrospective study was conducted of 245 patients with submucosal gastric cancer treated by gastrectomy combined with D_2 lymph node resection between 1985 and 1994 in a university hospital.

Results Lymph node metastasis was observed in 34 patients (14 per cent). The mortality rate due to recurrence in patients with lymph node metastasis (three of 34) was significantly higher than in those without lymph node metastasis (five (2 per cent) of 211) ($\chi^2 = 3{\cdot}95$, 1 d.f., $P < 0{\cdot}05$). Tumour size, depth of invasion, lymphatic involvement of cancer cells and preoperative diagnosis of advanced cancer correlated significantly with the presence of lymph node metastasis. When the submucosal carcinomas were classified into three categories according to depth of invasion by dividing the submucosal (sm) layer into three equal parts, sm1, sm2 and sm3, the incidence of lymph node metastasis increased from 2 per cent to 12 and 20 per cent respectively.

Conclusion When the pathological report reveals sm1 invasion after laparoscopic or endoscopic surgery, reoperation should not be necessary because sm1-carcinomas with diameters of less than 2 cm do not usually metastasize to the lymph nodes.

Recent progress in the diagnosis and surgical treatment of early gastric cancer has reduced the mortality rate associated with gastric cancer markedly, particularly as a result of improved early diagnosis of asymptomatic early gastric cancer[1]. In Japan, patients with early gastric cancer have a favourable prognosis after curative surgery with reported 5-year survival rates in excess of 90 per cent[2–5]. However, although early gastric carcinoma is potentially highly curable by surgical treatment, about 10 per cent of patients suffer recurrence after 'curative' operations for this cancer[6]. As such patients will survive for long periods, more attention should be focused on the relief of symptoms to improve the quality of life. In the authors' hospital, gastrectomy with D_2 lymph node dissection was the standard procedure for early gastric cancer until 1976. Gastrectomy with D_1 and no. 7 lymph node dissection was introduced for mucosal cancer in 1977, endoscopic mucosal resection was commenced in 1990, and laparoscopic surgery for mucosal cancer was instituted in 1992[7–10].

In this study, patients with early gastric cancer with submucosal invasion (sm-carcinoma) were investigated clinicopathologically in relation to the depth of invasion in the submucosal layer and lymph node metastasis, in order to establish the most appropriate treatment for sm-carcinoma.

Patients and methods

From 1985 to 1994, 245 patients with sm-carcinoma and no evidence of any other malignancy underwent gastrectomy with D_2 lymph node resection. All the cancers were diagnosed histopathologically as sm-carcinomas. The postoperative follow-up study was conducted in April 1995, when the cumulative mortality rate due to recurrence was calculated and the factors involved in death due to sm-carcinoma were investigated.

The clinicopathological study was based on the Japanese Classification of Gastric Carcinoma of the Japanese Research Society for Gastric Cancer[11]. Preoperative diagnoses were made on the basis of endoscopic and radiological findings, surgical specimens were reviewed by the chief surgeon when the operation was performed, and all pathological slides were reviewed by experienced pathologists in the authors' hospital. The macroscopic features of each gastric cancer were classified in terms of tumour location, macroscopic type and size. Microscopic features were classified according to histological type, infiltration pattern, tumour growth into the surrounding tissue, depth of invasion, lymphatic invasion, venous invasion and lymph node metastasis. Furthermore, submucosal invasion depth was divided into three categories, sm1, sm2 and sm3, by dividing the submucosal layer into three equal parts. All slides were submitted 'blindly' with respect to nodal status to the pathologists for determination of submucosal involvement. The recurrence pattern was determined by reviewing the medical records, including physical examination, laboratory data, ultrasonography and computed tomography findings.

Statistical analysis

The χ^2 test or Student's t test, as appropriate, was used for statistical analysis. The Kaplan–Meier method was used to estimate survival rates, and differences between them were assessed with the log rank test. Logistic regression analysis was used to evaluate risk factors for lymph node metastasis, with Cox's proportional hazards analysis to evaluate survival, using SAS software (SAS Institute, Cary, North Carolina, USA)[12,13]. $P < 0{\cdot}05$ was considered statistically significant.

Results

The clinicopathological findings are summarized in *Tables 1* and *2*. A total of 245 patients had early gastric cancer

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Table 1 Characteristics of patients according to the presence of lymph node metastasis

	Lymph node metastasis		
	Absent	Present	Total
Sex ratio (M:F)	161:50	22:12	183:62
Age (years)			
Mean(s.d.)	63(11)	64(37)	63(38)
Median	59	61	63
Distribution			
30–39	7 (88)	1 (12)	8
40–49	33 (94)	2 (6)	35
50–59	50 (82)	11 (18)	61
60–69	63 (88)	9 (12)	72
70–79	52 (85)	9 (15)	61
80–89	6 (80)	2 (20)	8
Death due to recurrence	5 (2)	3 (9)*	8
Total	211 (86)	34 (14)	245

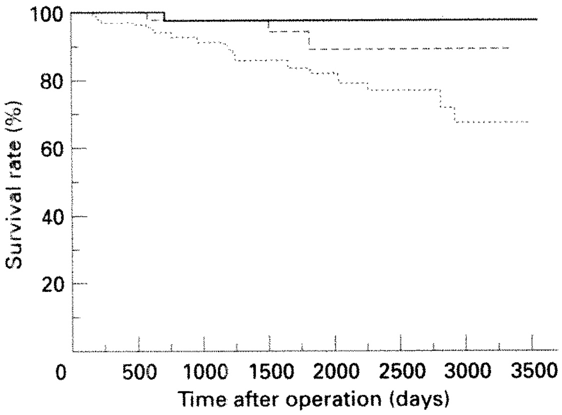
Values in parentheses are percentages unless otherwise stated. $^*P < 0{\cdot}05$ *versus* no lymph node metastasis (χ^2 test)

Table 2 Clinicopathological findings related to the presence of lymph node metastasis

	Lymph node metastasis		
	Absent ($n = 211$)	Present ($n = 34$)	P
Tumour location			
Lower	73 (83)	15 (17)	
Middle	113 (89)	14 (11)	n.s.
Upper	25 (83)	5 (17)	
Macroscopic type			
Early gastric cancer			
Elevated	15 (88)	2 (12)	
Depressed	142 (86)	23 (14)	n.s.
Mixed	43 (91)	4 (9)	
Total	200 (87)	29 (13)	$< 0{\cdot}05$*
Advanced gastric cancer	11 (69)	5 (31)	
Pathological diagnosis			
Histology			
Undifferentiated	83 (84)	16 (16)	n.s.
Differentiated	128 (88)	18 (12)	
Lymphatic involvement			
Absent	132 (96)	5 (4)	$< 0{\cdot}01$*
Present	79 (73)	29 (27)	
Vascular involvement			
Absent	201 (87)	30 (13)	n.s.
Present	10 (71)	4 (29)	
Infiltration			
α	37 (90)	4 (10)	
β	136 (86)	23 (14)	n.s.
γ	38 (84)	7 (16)	
Mean(s.d.) tumour diameter (cm)	3·1(2·0)	5·3(2·1)	$< 0{\cdot}001$†

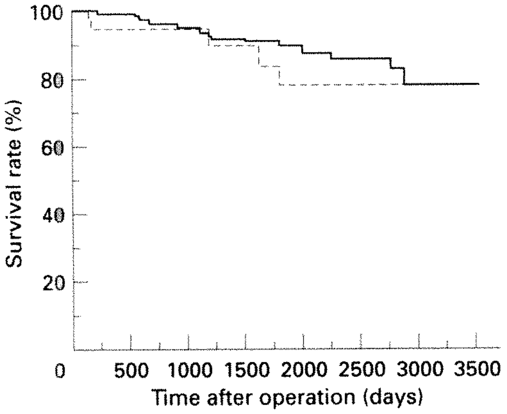
Values in parentheses are percentages unless otherwise stated. $^*\chi^2$ test; †Student's *t* test

with submucosal invasion. Lymph node metastasis was confirmed histologically in 34 patients (14 per cent). There were no significant differences between those with or without lymph node metastasis with respect to sex or age distribution (*Table 1*).



No. at risk								
sm1	60	51	30	22	14	8	2	
sm2	57	43	31	20	15	12	7	1
sm3	128	102	69	48	35	24	11	2

Fig. 1 Overall survival rate according to depth of submucosal invasion, expressed by dividing the submucosal (sm) layer equally into three parts: sm1 (———; $n = 60$), sm2 (– – –; $n = 57$) and sm3 (- - - - -; $n = 128$). $P < 0{\cdot}05$ (sm1-carcinoma *versus* sm3-carcinoma, log rank test)



No. at risk								
Node negative	211	170	111	74	52	35	15	1
Node positive	34	26	19	16	12	9	5	2

Fig. 2 Overall survival rate according to lymph node metastasis: ———, node negative ($n = 211$); – – –, node positive ($n = 34$)

Advanced gastric cancer was diagnosed before operation in 16 patients, five of whom had lymph node metastasis (*Table 2*), whereas 29 (3 per cent) of the 229 who were diagnosed before operation as having early gastric cancer had lymph node metastasis; these values were significantly different ($\chi^2 = 4{\cdot}32$, 1 d.f., $P < 0{\cdot}05$) (*Table 2*).

In patients with sm-carcinoma with lymph node metastasis, the incidence of lymphatic involvement was higher than in those without lymph node metastasis, but the incidence of venous involvement in these two groups did not differ significantly (*Table 2*).

Table 3 shows the incidence of lymph node metastasis according to the subdivision of submucosal invasion and lymph node metastasis. When lymph node metastasis was subcategorized from n1 to n4, no significant correlation

Table 3 Presence and level of lymph node metastasis categorized by depth of invasion and size of lesion

	Lymph node status						
	n0	n +	n1	n2	n3	n4	Total
Depth of invasion							
sm1	59 (98)	1 (2)*	1	0	0	0	60
sm2	50 (88)	7 (12)	6	1	0	0	57
sm3	102 (80)	26 (20)†	15	8	1	2	128
Total	211 (86)	34 (14)	22	9	1	2	245
Lesion size (cm)							
>0–2	81 (99)	1 (1) ‡	0	1	0	0	82
>2–4	83 (89)	10 (11)	6	3	0	1	93
>4–6	34 (71)	14 (29)	10	3	1	0	48
>6	13 (59)	9 (41)	6	2	0	1	22

sm, Submucosal. *$\chi^2 = 8{\cdot}61$, 1 d.f., $P < 0{\cdot}01$ *versus* sm2 and sm3; †$\chi^2 = 8{\cdot}19$, 1 d.f., $P < 0{\cdot}01$ *versus* sm1 and sm2; ‡$\chi^2 = 34{\cdot}59$, 3 d.f., $P < 0{\cdot}01$

between submucosal invasion and the extent of lymph node metastasis was found.

The incidence of lymph node metastasis in patients with sm1, sm2 and sm3 carcinomas was 2, 12 and 20 per cent respectively (*Table 3*). Metastasis was significantly more common in sm3-carcinoma than in sm1- and sm2-carcinoma (*Table 3*). Only one patient with sm1-carcinoma had lymph node metastasis (the primary tumour was 5·5 cm in diameter) and n3 and n4 lymph node metastases were found only in patients with sm3-carcinoma (*Table 3*).

The mean(s.d.) diameter of lesions with lymph node metastasis was significantly greater than that of those without lymph node metastasis (*Table 2*). Lesions were classified into four groups according to diameter and there was a progressive increase in nodal metastasis with increasing size (*Table 3*).

Eight patients with sm-carcinoma died from recurrence during the observation period, significantly more in the node-positive group (*Table 1*). As all the patients who died had sm3 invasion, sm3-carcinoma was thought to be the most important risk factor for death from recurrent carcinoma. Overall survival rates according to the subcategory of invasion depth are shown in *Fig. 1*. Patients with sm1-carcinoma showed a significant survival benefit compared with those with sm3-carcinoma ($P < 0{\cdot}05$).

The survival rates of the patients with and without lymph node metastasis did not differ significantly (*Fig. 2*). Multivariate analysis was performed using logistic regression analysis and Cox proportional hazards analysis. The independent risk factors for lymph node metastasis were large tumour size and the degree of submucosal involvement, as shown in *Table 4*. The risk of the lymph node metastasis of sm2- and sm3-carcinomas was higher than that of sm1-carcinoma ($P = 0{\cdot}02$, odds ratio 11·262). The independent prognostic effect of six factors for survival was evaluated by Cox's proportional hazards analysis as shown in *Table 5*. The important factors for survival were submucosal involvement, vascular involvement and age.

Discussion

In Japan the prognosis of patients with early gastric cancer is very favourable after curative gastrectomy with lymph node dissection. Reported 5-year survival rates exceed 90 per cent[2–5]. However, lymph node metastasis, large tumours, submucosal invasion and lymphatic involvement of cancer cells remain risk factors for recurrence of early gastric cancer[9,14–22]. Recently, 'non-gastrectomy' procedures have been performed for small mucosal gastric cancer (m-carcinoma), including endoscopic mucosal resection and laparoscopic surgery[23,24]. In the authors' institution, laparoscopic surgery is indicated for type IIa cancers smaller than 2·5 cm in diameter and type IIc cancers of less than 1·5 cm without ulceration, and endoscopic mucosal resection is carried out for tumours smaller than 1 cm in diameter without ulcer scars[9,10]. To select the most appropriate operative procedures for mucosal gastric cancer, the depth of cancer invasion must be evaluated before operation using flexible endoscopy and gastrointestinal radiography. In addition, the introduction of endoscopic ultrasonography with a 20-MHz sonoprobe system[25] has increased diagnostic accuracy, as it enables mucosal and submucosal invasion by early gastric cancer to be differentiated. Such precise preoperative diagnostic methods will result in improved quality of life for these patients without reducing curability.

At present, the standard treatment in the authors' institution for sm-carcinoma is radical gastrectomy with

Table 4 Logistic regression analysis for factors associated with lymph node metastasis in early gastric cancer with submucosal invasion

Factor*	β	Standard error	P	Odds ratio
Age (older)	0·0270	0·0186	0·1467	1·027 (0·991–1·066)
Submucosal penetration (sm2 and sm3, sm1)	2·4214	1·0672	0·0233	11·262 (1·391–91·203)
Tumour size (per cm)	0·4120	0·0892	0·0001	1·510 (1·268–1·798)
Macroscopic type (advanced gastric cancer, early gastric cancer)	1·1687	0·6498	0·0721	3·218 (0·900–11·499)
Pathological diagnosis (differentiated, undifferentiated)	0·5787	0·4427	0·1912	1·784 (0·749–4·248)

Values in parentheses are 95 per cent confidence intervals. *Observed values are shown in parentheses. sm, Submucosal

Table 5 Cox proportional hazards analysis for factors influencing survival in early gastric cancer with submucosal invasion

Prognostic variable*	β	Standard error	P	Risk ratio
Age (older)	0·0567	0·0223	0·0109	1·058 (1·013–1·106)
Submucosal penetration (sm3)	1·2535	0·5794	0·0305	3·503 (1·125–10·904)
Vascular involvement (present)	0·8247	0·3688	0·0253	2·281 (1·107–4·700)
Tumour size (per cm)	−0·0305	0·1179	0·7956	0·970 (0·770–1·222)
Lymph node involvement (present)	0·8470	0·7059	0·2302	2·333 (0·585–9·304)
Macroscopic type (advanced gastric cancer)	0·2032	0·5987	0·7343	1·225 (0·379–3·962)

Values in parentheses are 95 per cent confidence intervals. *Detrimental factors are shown in parentheses. sm, Submucosal

D_2 lymph node dissection[8,26,27]. If sm-carcinomas without lymph node metastasis could be identified before operation, the indications for local resection could possibly be extended to some subcategories of sm-carcinoma. In this study the clinicopathological features of sm-carcinoma in relation to lymph node metastasis and prognosis were investigated.

Initially, the risk factors for lymph node metastasis of early gastric cancer with submucosal invasion were analysed, because the most important factor related to the prognosis associated with sm-carcinoma appears to be lymph node metastasis. Using univariate and multivariate analysis, high-risk factors for lymph node metastasis of sm-carcinoma were found to be large tumours and deep invasion. Furthermore, important factors for survival using Cox's proportional hazards model were the degree of submucosal involvement, vascular involvement and age. Hioki *et al.*[23] found that lymph node metastasis was common in patients with submucosal or elevated early gastric cancer, particularly if the lesion diameter exceeded 4 cm. Boku *et al.*[28] reported that lymph node metastasis occurred more frequently with protruded-type cancer with a diameter greater than 3 cm and submucosal invasion. Maehara *et al.*[14] reported that independent risk factors for the occurrence of lymph node metastasis included large tumours, submucosal invasion and lymphatic involvement by tumour cells.

When sm-carcinomas were classified into three groups by dividing the submucosal layer into three equal parts (sm1, sm2 and sm3), lymph node metastasis in the sm1 layer was limited to level 1, although 11 of 26 metastases in the sm3 layer were at more than level 2. When the sm-carcinomas were classified into four groups according to diameter, the incidence of metastases increased significantly depending on the lesion size. These findings suggest that patients with sm-carcinoma invading to the depth of sm1 and with a diameter of 2 cm or less could be treated by modified radical gastrectomy, although those with sm3 layer invasion should undergo standard radical gastrectomy with D_2 dissection of lymph nodes.

Recently, the accuracy of preoperative diagnosis of the depth of cancer invasion has improved, owing to the widespread use of endoscopic ultrasonography in Japan, and m- and sm-carcinomas can now be differentiated[25,29,30]. With a 20-MHz sonoprobe system the diagnostic accuracy in differentiating mucosal and submucosal invasion has increased to 88·9 per cent[25].

However, because it is difficult to determine the sm-carcinoma subclass before operation, the authors suggest performing standard gastrectomy with D_2 lymph node dissection for patients with a preoperative diagnosis of sm-carcinoma. In addition, as patients with large sm3-carcinomas are at high risk for developing level 2 lymph node metastasis, adjuvant chemotherapy may be indicated for such patients. However, it should not be necessary to reoperate on patients if the pathological reports reveal sm1-carcinoma after they have been treated with laparoscopic or endoscopic surgery.

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Preoperative risk analysis and postoperative mortality of oesophagectomy for resectable oesophageal cancer

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Background Postoperative mortality after oesophagectomy for oesophageal cancer depends largely on the preoperative physiological status of the patient.

Methods A composite scoring system to predict the risk of oesophagectomy based on objective preoperative parameters was developed based on a retrospective review of patients operated on and evaluated prospectively in two subsequent patient groups.

Results An initial retrospective multivariate analysis of 432 patients who had oesophagectomy identified a compromised general status ($P < 0{\cdot}001$) and poor cardiac ($P < 0{\cdot}001$), hepatic ($P < 0{\cdot}05$) and respiratory ($P < 0{\cdot}05$) function as independent predictors of a fatal postoperative course. Based on the relative risk associated with the individual impaired organ functions, a composite risk score was established. A prospective study in 121 patients confirmed that this composite scoring system provides a better identification of high-risk patients than any of the individual parameters. Inclusion of the composite score into the process of patient selection and choice of the procedure resulted in a decrease of postoperative mortality rate from 9·4 per cent (52 of 553) to 1·6 per cent (four of 252) ($P < 0{\cdot}001$).

Conclusion The risk of death after oesophagectomy for oesophageal cancer can be assessed objectively before surgery and quantified by a composite risk score. This score provides a useful tool for refining the criteria of patient selection for resection or the choice of procedure.

Despite recent advances with other therapeutic modalities, surgical resection provides the only chance of cure for patients with oesophageal carcinoma. For both squamous and adenocarcinoma of the oesophagus, the 5-year survival rate after complete surgical tumour resection (i.e. a Union Internacional Contra la Cancrum R_0 resection[1]) is of the order of 40 per cent in those who survive the procedure[2,3]. Oesophagectomy therefore remains the mainstay of therapy in patients with potentially resectable oesophageal cancer. Morbidity and mortality associated with oesophagectomy are, however, substantial. In a review of recent series the mean mortality rate from oesophagectomy for cancer was 13 per cent independent of the surgical approach[4] and even in experienced centres the postoperative mortality rate ranges between 5 and 10 per cent in the Western world[4].

Several analyses have shown that, after standardization of surgical resection and reconstruction techniques, the severity of the postoperative course and postoperative mortality depend largely on the preoperative physiological status of the patient[5,6]. The physiological status is, however, often markedly reduced in patients with oesophageal cancer. As hyperalimentation and other attempts to improve the general status of these patients before operation have failed to show any benefit[7,8], a reduction in the postoperative mortality rate can be achieved only by strict selection of patients who have adequate physiological reserve to withstand an extended surgical procedure and a potentially prolonged and complicated postoperative course.

None of the currently available scoring systems is applicable to the specific problems associated with oesophagectomy and reconstruction[9]. Most surgeons therefore rely on the 'impression' of the patient and their own 'experience' rather than objective parameters for the selection of patients for oesophagectomy. Nevertheless, in a recent consensus conference of the International Society for Diseases of the Esophagus held in August 1995 in Milan, all of the participating experts agreed on the importance of objective preoperative risk analysis to improve the outcome of surgical resection for oesophageal cancer[9]. In the present study an attempt was made to develop a composite scoring system which allows prediction of the risk of oesophagectomy for cancer based on objective preoperative physiological parameters. Three specific questions were addressed. (1) Can a detailed preoperative assessment identify individual physiological parameters (i.e. risk factors) that correlate with the postoperative course? (2) Can the risk for postoperative death after oesophagectomy be predicted with a risk score based on individual preoperative physiological parameters? (3) Can the clinical use of such a scoring system reduce the mortality rate of oesophagectomy?

Patients and methods

Patients

Between June 1982 and December 1996 a total of 805 patients with oesophageal cancer underwent oesophagectomy with curative intent. All patients had a detailed preoperative assessment of their general status, organ function and tumour stage according to the parameters listed in *Table 1*. All data from the preoperative assessment and postoperative course were documented prospectively in a database.

The mode and extent of resection were standardized and determined by the location and histological type of tumour as described elsewhere[2,3]. A radical transmediastinal resection with *en bloc* lymphadenectomy of the lower posterior mediastinum and upper abdomen (compartment II) was performed for

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Table 1 Parameters used for preoperative functional assessment of patients with oesophageal cancer

- General status
  - Sex
  - Age
  - Karnofsky index[10] (0–100 per cent)
  - History of alcohol abuse ('yes' or 'no')
  - History of tobacco abuse ('yes' or 'no')
  - Weight loss (percentage of body-weight)
  - 'Mental cooperation' of the patient ('good' or 'poor')
- Pulmonary function
  - Vital capacity (percentage of normal)
  - Forced expiratory volume (FEV$_1$; percentage of normal)
  - Peak flow (percentage of normal)
  - P_{aO_2} (mmHg)
  - P_{aCO_2} (mmHg)
- Hepatic function
  - Serum albumin (g/dl)
  - Serum bilirubin (mg/l)
  - Partial thromboplastin time (s)
  - Aminopyrine breath test[11]
  - Cirrhosis ('yes' or 'no')
- Renal function
  - Creatinine clearance (ml/min)
- Cardiac function
  - Electrocardiogram ('abnormal' or 'normal')
  - Chest radiograph ('abnormal' or 'normal')
  - Cardiologist's evaluation with further detailed testing as indicated ('normal risk', 'increased risk' or 'high risk')
- Diabetes
  - 'Yes' or 'no'
- Tumour stage (based on standard staging techniques[12,13])
  - Locoregional (T$_1$ or T$_2$) or locally advanced (T$_3$ or T$_4$)

P_{aO_2}, arterial partial pressure of oxygen; P_{aCO_2}, arterial partial pressure of carbon dioxide

Table 2 Classification of the postoperative course

- Normal
  - Mechanical ventilation for less than 48 h
  - ICU treatment for less than 7 days
- Prolonged
  - Mechanical ventilation for 48 h to 7 days, or ICU treatment for 7–21 days
- Severe
  - Mechanical ventilation for more than 7 days, or ICU treatment for more than 21 days, or readmission to the ICU
- Fatal
  - Death within 30 days

ICU, intensive care unit

adenocarcinoma of the distal oesophagus, while a transthoracic *en bloc* resection with extended two-field lymphadenectomy was performed for squamous cell oesophageal cancer of the intrathoracic oesophagus. A gastric tube was used for reconstruction in 713 patients; transverse or left hemicolon was used for reconstruction in 84 patients. The oesophagointestinal anastomosis was performed in the neck in 756 of 805 patients. Patients with cervical oesophageal cancer and those who had resection with palliative intention were excluded from the study. The postoperative course was classified in each patient as defined in *Table 2*.

Study design

The study was performed in three phases. In phase I of the analysis each of the parameters documented before operation (*Table 1*) was correlated retrospectively to the severity of the postoperative course (*Table 2*) in 432 patients (377 men, 55 women; mean age 56·7 years) who had oesophagectomy between June 1982 and December 1991. Discriminant analysis was performed to select the best cut-off points for the parameters with an independent effect on multivariate analysis. Based on the established parameters, preoperative organ function was then estimated as 'normal', 'compromised' or 'severely impaired'. The impact of individual organ dysfunction on postoperative mortality was subsequently assessed by regression analysis and a composite score incorporating the weighted risk of each individual organ system for postoperative mortality was established.

In phase II of the analysis the clinical value of the composite risk score to predict postoperative mortality was assessed prospectively in 121 patients (106 men, 15 women; mean age 57·9 years) who had oesophagectomy for oesophageal cancer between January 1992 and December 1993. During phase I and phase II of the analysis, the decision to perform oesophagectomy was based solely on the judgement of the responsible surgeons. In December 1993 the results of phases I and II of the study were made known to all surgeons performing oesophagectomy.

From January 1994 to December 1996 (phase III of the study) the composite risk score of each patient was included in the decision-making process for selection for surgical resection and selection of the procedure. During this period patients with a high risk for postoperative death, based on the preoperative risk score, were referred for other modes of treatment or had oesophageal resection with two-stage reconstruction of the continuity of the alimentary tract (i.e. usually after 4 weeks). In the authors' experience, two-stage reconstruction is a safer way to perform oesophageal resection and reconstruction in high-risk patients (unpublished data). During this period oesophagectomy with primary reconstruction was performed in 211 patients (182 men, 29 women; mean age 58·4 years), and a delayed reconstruction after oesophagectomy was chosen in 41 patients (33 men, eight women; mean age 61·2 years). Non-surgical treatment modalities were used in 24 patients with potentially resectable oesophageal cancer but a high risk score on preoperative analysis.

Statistical analysis

All statistical analyses were performed with the BMDP (Los Angeles, California, USA) Statistical Software Package[14]. $P<0{\cdot}05$ was considered statistically significant.

Results

Multivariate analysis showed a significant correlation between the severity of the postoperative course and the preoperative Karnofsky index, the estimated mental 'cooperation' of the patient, vital capacity, arterial partial pressure of oxygen (P_{aO_2}), the aminopyrine breath test, the presence of cirrhosis, and an increased cardiac risk based on the cardiologist's judgement. The cut-off values that provided the best separation between a normal–prolonged and a severe–fatal postoperative course are shown in *Table 3*. Age, sex, tumour stage, presence of diabetes, renal function, and history of alcohol or tobacco abuse had no independent effect on the postoperative course.

Based on the established parameters, hepatic, cardiac and pulmonary function and the general status of the patient were classified individually as 'normal', 'compromised' or 'severely impaired' as shown in *Table 4*. Retrospective application of these organ scores to the 432 patients treated during phase I of the study (June 1982 to December 1991) confirmed a significantly increased postoperative mortality rate for patients with a severely impaired general status (relative risk 3·6, $P<0{\cdot}001$) followed by poor cardiac function (relative risk 2·8, $P<0{\cdot}001$), poor hepatic function (relative risk 2·1,

$P < 0\cdot05$) and impaired respiratory function (relative risk $1\cdot7$, $P < 0\cdot05$).

To create a composite risk score of all relevant parameters, a weighting factor was established based on the relative risk associated with each individual factor. This factor was: general status × 4, cardiac function × 3, hepatic function × 2 and respiratory function × 2. Multiplication of this weighting factor with the individual score for preoperative cardiac, hepatic and respiratory function and general status (*Table 4*), and summation of the results, creates a single composite score ranging between 11 total score points for a patient without any risk factors and 33 for a patient with the highest risk in all relevant parameters. Discriminant analysis showed that this composite scoring system provided a separation of patients into three distinct risk groups for postoperative mortality when applied to the group of patients from which it was derived. The postoperative 30-day mortality rate was $3\cdot6$ per cent in the 166 patients with 11–15 points ('low risk'), $8\cdot7$ per cent in the 194 with 16–21 score points ('moderate risk') and 28 per cent in the 72 with 22–33 score points ('high risk') ($P < 0\cdot05$ between all groups).

Table 3 Cut-off values for individual independent continuous parameters that provide the best separation between a normal–prolonged and a severe–fatal postoperative course after oesophagectomy (discriminant analysis in 432 patients undergoing oesophagectomy between June 1982 and December 1991)

	Parameter value	P*
Karnofsky index	80%	$< 0\cdot001$
Aminopyrine breath test	$0\cdot4$	$< 0\cdot05$
Vital capacity	90%	$< 0\cdot05$
P_{aO_2}	70 mmHg	$< 0\cdot05$

P_{aO_2}, arterial partial pressure of oxygen. *χ^2 test

Table 4 Classification of individual organ dysfunction based on multivariate analysis of the postoperative course after oesophagectomy

	Value or finding
Pulmonary function	
1 Normal	VC > 90% and P_{aO_2} > 70 mmHg
2 Compromised	VC < 90% or P_{aO_2} < 70 mmHg
3 Severely impaired	VC < 90% and P_{aO_2} < 70 mmHg
Hepatic function	
1 Normal	ABT > $0\cdot4$
2 Compromised	ABT < $0\cdot4$, no cirrhosis
3 Severely impaired	Cirrhosis
Cardiac function (based on cardiologist's impression)	
1 Normal	Normal risk for major surgical procedure
2 Compromised	Increased risk for major surgical procedure
3 Severely impaired	High-risk patient for major surgical procedure
General status	
1 Normal	Karnofsky index > 80% and 'good' cooperation
2 Compromised	Karnofsky index ≤ 80% or 'poor' cooperation
3 Severely impaired	Karnofsky index ≤ 80% and 'poor' cooperation

ABT, aminopyrine breath test; VC, vital capacity; P_{aO_2}, arterial partial pressure of oxygen

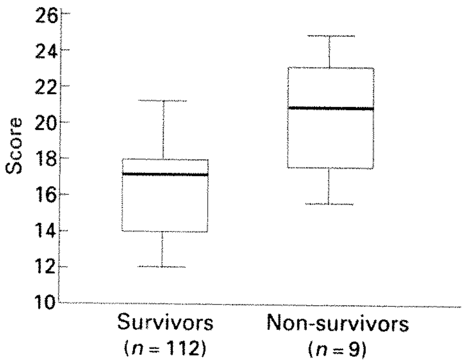

Fig. 1 Median and interquartile range of the composite risk score in 112 patients who survived oesophagectomy for cancer and in the nine who died within 30 days of the procedure during phase II of the study. $P < 0\cdot01$ (survivors *versus* non-survivors, Mann–Whitney U test). Whiskers indicate standard deviation

Prospective evaluation of this composite scoring system in 121 consecutive patients undergoing oesophagectomy for oesophageal cancer between January 1992 and December 1993 (phase II of the analysis) confirmed the validity of the scoring system in predicting the postoperative course. Postoperative 30-day mortality rate was 2 per cent in the 46 patients classified as 'low risk' (11–15 score points), 5 per cent in the 55 classified as 'moderate risk' (16–21 score points) and 25 per cent in the 20 classified as 'high risk' (22–33 score points; $P < 0\cdot01$ *versus* low risk and $P < 0\cdot05$ *versus* moderate risk). The median score value was 17 in 112 patients who survived the procedure compared with a median of 21 in the nine who died during the postoperative course ($P < 0\cdot01$) (*Fig. 1*). Of the nine patients who died after operation, five were classified as 'high risk' on preoperative assessment (risk score of 22 more).

Use of two-stage reconstruction in moderate and high-risk patients or complete exclusion of these patients from oesophagectomy (*Table 5*) resulted in a marked decrease in the postoperative mortality rate to below 2 per cent in this department after January 1994, although the

Table 5 Prevalence of one-stage surgery (resection and immediate reconstruction), two-stage surgery (resection and delayed reconstruction) and non-operative therapy in patients with potentially resectable oesophageal cancer in the various risk groups during phase III of the study, during which the composite risk score was included in the process of patient selection and choice of procedure

Risk group	No. of patients with 'one-stage' surgery	No. of patients with 'two-stage' surgery	No. of patients treated without operation
'Low risk' ($n = 111$)	111 (1)	0	0
'Moderate risk' ($n = 125$)	98 (1)	25 (1)	2
'High risk' ($n = 40$)	2	16 (1)	22
Total	211	41	24

Values in parentheses show patients who died after operation, giving a postoperative 30-day mortality rate of $1\cdot6$ per cent (four of 252 patients)

Table 6 Prevalence of 'high-risk' patients*, patients with locally advanced tumours (T_3 or T_4) and postoperative mortality from oesophagectomy for oesophageal cancer performed between 1982 and 1996

Time interval	Total no. of oesophageal resections	Prevalence of advanced tumours (T_3 or T_4)	Prevalence of 'high-risk' patients	Postoperative 30-day mortality	Postoperative 90-day mortality
Phase I					
June 1982 to December 1985	82	53 (65)	11 (13)	8 (10)	13 (16)
January 1986 to December 1987	121	73 (60·3)	22 (18·2)	13 (10·7)	20 (16·5)
January 1988 to December 1989	112	65 (58·0)	18 (16·1)	9 (8·0)	14 (12·5)
January 1990 to December 1991	117	72 (61·5)	21 (17·9)	13 (11·1)	19 (16·2)
Phase II					
January 1992 to December 1993	121	68 (56·2)	20 (16·5)	9 (7·4)	15 (12·4)
Phase III					
January 1994 to December 1995	163	97 (59·5)	12 (7·4)	3 (1·8)	8 (4·9)
January 1996 to December 1996	89	54 (61)	6 (7)	1 (1)	5 (6)

Values in parentheses are percentages. *Preoperative risk score of 22 or higher

prevalence of patients with advanced tumour stages remained unchanged (*Table 6*).

Discussion

Experience and training of the surgeon and the physiological status of the patient have been clearly identified as the main risk factors affecting the mortality rate after oesophagectomy for oesophageal cancer[5,6,9,15]. Postoperative mortality rates in experienced centres can be reduced further only by better selection of patients with sufficient physiological reserve to withstand the extended surgical procedure and a potentially complicated postoperative course. The present study shows that the risk of postoperative death in patients with resectable oesophageal cancer is determined in decreasing order by the preoperative general status, cardiac function, hepatic function and respiratory function. Objective assessment of preoperative function of these organ systems and calculation of a composite score based on the relative impact of each individual parameter allowed 'low', 'moderate' and 'high' risk groups for oesophageal resection to be established. This score thus provides an objective instrument for patient selection.

General status has been difficult to categorize objectively[5,9,16,17]. The estimation of the patient's mental 'cooperation' by the surgeon is undoubtedly subjective and introduces a non-quantifiable aspect into the proposed score. Attribution of 'poor' or 'good' cooperation alone, without other objective parameters, did not result in marked alteration of the total composite score.

Pulmonary and cardiac complications account for up to 70 per cent of postoperative deaths after oesophagectomy[5,16–20]. This is reflected in the rather high multiplier attributed to cardiac dysfunction in the composite score. A detailed cardiological evaluation is therefore recommended in any patient considered for oesophagectomy in whom the history, physical examination, standard electrocardiogram or chest radiograph show any abnormality. Spirometry has not been found consistently useful to predict pulmonary complications after major surgery[16,19]. The present and other analyses[5,21] show that the vital capacity in combination with P_{aO_2} allows identification of patients with an increased risk of postoperative death after oesophagectomy. Routine preoperative objective pulmonary function tests are therefore recommended before considering oesophagectomy.

Decompensated liver cirrhosis is considered a contraindication for oesophageal resection in many centres. An independent effect of hepatic dysfunction on the postoperative mortality rate is confirmed in the present study. This study shows that the aminopyrine breath test, which assesses hepatic cytochrome *P*450 function, allows identification of patients at increased risk of postoperative death even in the absence of frank cirrhosis[11]. This non-invasive and easy test should therefore be included in the assessment of hepatic function in any patient considered for oesophageal resection.

In contrast to other reports[5,6] tumour stage and patient age did not predict postoperative death in the present analysis. This is most likely because of the extensive preoperative tumour staging performed at this institution, which usually allowed identification and exclusion of patients with metastatic or irresectable tumours before operation. In contrast to other centres[5], palliative resection is not performed as less invasive palliative options are readily available. This study further shows that advanced age alone is not associated with an increased risk of postoperative death. Similar to the experience reported by Peracchia *et al.*[22], the present authors therefore believe that the benefits of potentially curative resection should not be withheld from an otherwise fit patient with a resectable tumour simply because of advanced age. Moreover, recent experience has shown that potentially curative resection in high-risk patient groups can be made safer by a two-stage procedure (oesophageal resection with delayed reconstruction of alimentary tract continuity). A similar experience with two-stage reconstruction in high-risk patients has been reported from Japan[23].

In summary, the present study shows that the risk of oesophagectomy in patients with potentially resectable oesophageal cancer can be assessed objectively before operation and quantified by a composite risk score. Strict inclusion of the risk score in the preoperative decision-making process resulted in a marked decrease of the postoperative mortality rate at this institution, to below 2 per cent. This risk score may therefore be used to refine the criteria of patient selection for resection or the choice of procedure.

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Abdominal and dyspeptic symptoms in patients with peptic ulcer treated medically or surgically

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Background Abdominal and dyspeptic complaints, which are prominent symptoms in patients with peptic ulceration, are commonly reported in the general population. There are few reports of follow-up study of peptic ulcer therapies in which clinical outcome has been compared with symptom reporting in community controls.

Methods Three populations of patients with peptic ulcer disease (patients who had elective proximal gastric vagotomy (PGV), those having PGV for emergency indications and those receiving medical treatment with H_2-receptor antagonists) were included in a questionnaire survey and compared with a group of randomly selected community controls.

Results The vagotomized patients reported fewer abdominal complaints ($P = 0\cdot0003$) and fewer dyspeptic complaints lasting for more than 1 week ($P = 0\cdot05$) than those treated medically. There was no significant difference between vagotomized patients and community controls in the reporting of abdominal ($P = 0\cdot2$) or dyspeptic ($P = 0\cdot9$) complaints.

Conclusion Taking abdominal complaints as the endpoint for former peptic ulcer treatment, surgical treatment with PGV seemed to be superior to therapy with H_2-receptor antagonists and produced an almost identical level of complaints to that seen in the community population.

Ulcer healing or recurrence has been the major endpoint in clinical trials evaluating peptic ulcer treatment. This has nowadays been more or less replaced by verified eradication of *Helicobacter pylori* infection, as removal of these bacteria from the gastric mucosa prevents ulcer recurrence[1,2]. There are surprisingly few reports comparing the long-term outcome of surgical and medical peptic ulcer treatment[3–7] using abdominal or dyspeptic complaints as clinical endpoints[8]. So far only one study[9] has incorporated abdominal complaints in healthy control subjects when investigating the clinical results following proximal gastric vagotomy (PGV). Patients after operation and those with peptic ulcer disease may have several reasons for dyspepsia. Treating the peptic ulcer disease may take away only one, or some, of several reasons for dyspeptic symptoms. For this reason, population controls should be mandatory when assessing clinical outcome of peptic ulcer treatment regimens. There appears to be no report contrasting the level of abdominal or dyspeptic complaints in medically or surgically treated patients with peptic ulceration with that of similar symptoms in the community population.

This study was designed to compare the long-term outcome in surgically or medically treated patients with peptic ulceration with that in a matched group of randomly selected non-ulcer subjects as a reference group using abdominal and dyspeptic complaints as the clinical endpoint.

Patients and methods

The study was performed as a postal questionnaire survey in three differently treated groups of patients with verified peptic ulcer disease. Patients who underwent PGV electively ($n = 368$) or as an emergency operation ($n = 130$) in the period from 1967 to 1990, and who were still alive on 1 January 1995, were identified from operating theatre records ($n = 721$). All those with peptic ulcers verified by endoscopic or radiological examination in the period from 1979 to 1986 and who had received only acid suppression medication were included as medically treated patients. From the National Population Register 762 healthy community controls were selected randomly and matched to the surgically treated patients for mean age and sex distribution.

All four groups received an identical questionnaire on abdominal complaints regarding type of abdominal discomfort or pain, its frequency and duration, consequences of the complaints on working ability, social life, quality of life and use of health services. The questionnaire also surveyed the patients' self-reported health condition, contemporary complaints or illnesses, family history of abdominal diseases, socioeconomic status, eating habits, consumption of coffee, tea, alcohol and drugs, and smoking.

Table 1 Population characteristics of surgically or medically treated patients with peptic ulceration and of community controls

	Patients with peptic ulcer			
	Emergency PGV	Elective PGV	Medication	Controls
No. of patients	75	193	134	322
Age (years)				
Median	62·0	59·0	55·5	60·0
Range	28–87	29–85	36–72	47–75
Mean(s.d.)	61·8(14·2)	58·9(13·4)	54·3(9·1)	59·7(7·3)
Sex ratio (F:M)	23:52	45:148	46:88	90:232
Mean (range) length of follow-up (years)	11·4 (4–19)	12·9 (4–21)	11·3 (8–15)	—

PGV, proximal gastric vagotomy

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Table 2 Frequency of reported abdominal complaints among surgically or medically treated patients with peptic ulcer and in community controls

	Patients with peptic ulcer			
	Emergency PGV ($n = 75$)	Elective PGV ($n = 193$)	Medication ($n = 134$)	Controls ($n = 322$)
Abdominal complaint	43 (31–55)	56·0 (48·7–63·1)	74·6 (66·4–81·7)	57·5 (52·1–62·9)
No complaint	57 (45–69)	44·0 (36·9–51·3)	25·4 (18·3–33·6)	42·5 (37·1–47·9)
Any abdominal complaint lasting more than 1 week	31 (20–42)	39·9 (32·9–47·2)	42·5 (34·0–51·4)	46·3 (40·8–51·7)
Dyspeptic complaint lasting more than 1 week*	8 (3–17)	14·5 (9·9–20·3)	20·1 (13·7–27·9)	12·1 (8·6–15·7)
Abdominal pain at any location	23 (14–34)	36·8 (30·0–44·0)	70·1 (61·6–77·7)	18·0 (13·8–22·2)
Heartburn	20 (12–31)	25·4 (19·4–32·1)	47·0 (38·3–55·8)	24·2 (19·5–28·9)
Regurgitation	25 (16–37)	26·9 (20·8–33·8)	50·7 (42·0–59·5)	22·7 (18·1–27·2)
Ulcer recurrence	11 (5–20)	14·5 (10·0–20·5)	21·6 (15·0–29·6)	—

Values are percentages (95 per cent confidence interval). PGV, proximal gastric vagotomy. *Persistent or recurrent abdominal pain or discomfort located in the upper abdomen

Table 3 Frequency of abdominal complaints lasting for more than 1 week among surgically or medically treated patients with peptic ulcer and in community controls

	Patients with peptic ulcer			
	Emergency PGV	Elective PGV	Medication	Controls
Any abdominal complaints lasting more than 1 week*	23 of 75 (31)	77 of 193 (39·9)	57 of 134 (42·5)	149 of 322 (46·3)
Frequency of complaints†				
Daily	13 (3–34)	20·8 (12·4–31·5)	23·6 (13·2–37·0)	22·8 (16·3–30·4)
Every week	17 (5–39)	32·5 (22·2–44·1)	23·6 (13·2–37·0)	22·8 (16·3–30·4)
Every month	30 (13–53)	18·2 (10·3–28·6)	18·2 (9·1–30·9)	22·8 (16·3–30·4)
Less than every month	39 (20–62)	28·6 (18·8–40·0)	34·5 (22·2–48·6)	31·5 (24·2–39·7)

*Values in parentheses are percentages; †values are percentages (95 per cent confidence interval). PGV, proximal gastric vagotomy

Table 4 Reported influence of abdominal complaints on self-assessed working capacity among surgically or medically treated patients with peptic ulcer and in community controls

	Patients with peptic ulcer			
	Emergency PGV	Elective PGV	Medication	Controls
No. of patients*	71	177	118	275
Any abdominal complaint	43 (31–55)	56·0 (48·7–63·1)	74·6 (66·4–81·7)	57·5 (52·1–62·9)
Influence on working capacity				
None	76 (64–85)	63·8 (56·3–70·9)	50·0 (40·7–59·3)	78·5 (73·7–83·4)
Some	17 (9–28)	20·3 (14·7–27·0)	38·1 (29·3–47·5)	14·5 (10·4–18·7)
Significant	6 (2–14)	13·6 (8·9–19·5)	11·0 (6·0–18·1)	5·5 (3·1–8·8)
Unable to work	1 (0–8)	2·3 (0·6–5·7)	0·8 (0·0–4·6)	1·5 (0·4–3·7)

Values are percentages (95 per cent confidence interval). *Only patients with paid employment were included. PGV, proximal gastric vagotomy

Those who did not answer within 1 month received a postal reminder. There was no financial gain or hint of health benefits associated with participation in the survey.

The questionnaire was composed of questions used previously in the Sørreisa gastrointestinal disorder study[10] and was constructed as described by Eypasch *et al.*[11]. Approximately 80 per cent (range 80·0–81·0 per cent) of patients in each group returned the questionnaire. After exclusion of those providing incomplete answers, reporting biliary disease now or previously, or having had any abdominal operation for reasons other than peptic ulceration, 193 elective and 75 emergency PGV responders, 134 medically treated patients and 322 community control responders were included in the final analysis.

Abdominal complaints were defined as the reporting of one or more of the following symptoms: abdominal pain or discomfort independent of localization or duration, heartburn, regurgitation, nausea, retching or borborygmia without bowel disturbances.

Dyspeptic complaints were defined as persistent or recurrent abdominal pain or discomfort centred in the upper abdomen. This definition was used to distinguish patients with mainly epigastric discomfort and pain as the main symptoms from those with heartburn as the main symptom[12]. By these definitions the entity 'dyspeptic complaints' represents a subgroup of the entity 'abdominal complaints'.

Bowel disturbances were defined as diarrhoea and/or constipation.

Table 5 Frequency of antiulcer drug use during follow-up among surgically or medically treated patients with peptic ulcer and in community controls

	Patients with peptic ulcer			
	Emergency PGV ($n = 75$)	Elective PGV ($n = 193$)	Medication ($n = 134$)	Controls ($n = 322$)
No drugs	76 (65–85)	65·3 (58·1–72·0)	37·3 (29·1–46·1)	72·7 (67·8–77·5)
Antacids	22 (13–33)	31·1 (24·6–38·2)	55·2 (46·4–63·8)	25·5 (20·7–30·2)
H_2-receptor antagonists*	10 (4–18)	19·9 (14·4–26·4)	39·6 (31·2–48·4)	4·0 (2·2–6·8)
Proton pump inhibitors†	3 (0–10)	4·4 (1·9–8·4)	5·2 (2·1–10·5)	0·6 (0·1–2·2)
Other‡	1 (0–7)	10·5 (6·6–15·8)	6·0 (2·6–11·4)	2·8 (1·3–5·2)

Values are percentages (95 per cent confidence interval). *Cimetidine, famotidine or ranitidine; †omeprazole or lansoprazole; ‡prescribed drugs such as sucralfate, anticholinergic agents, tricyclic antidepressant (trimipramine) or prokinetic agent (cisapride). PGV, proximal gastric vagotomy

Dumping syndrome was defined as dizziness and fatigue after meals.

Statistical analysis

The proportion of patients answering the different questions in the questionnaires was calculated as a percentage with 95 per cent confidence intervals based on a normal distribution. The χ^2 test with Yates' correction was applied when comparing dichotomous variables.

The calculations were performed using the microcomputer software Confidence Interval analysis (BMJ Publishing Group, London, UK)[13] and Epi Info 6 (WHO Shareware, Geneva, Switzerland)[14].

The study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services.

Results

The mean age of medically treated patients was 4·6 and 7·5 years lower than those operated on as an emergency and electively respectively. The age range in the control population was 47–75 years compared with 28–87 years in surgically treated patients. Mean age in the control group was close to that of the surgically treated groups, but the age range was smaller (*Table 1*).

Most of the emergency operations (64 per cent) were for massive ulcer bleeding; 36 per cent of patients had a vagotomy for perforated ulcer. Of these, 48 per cent had a duodenal ulcer and 52 per cent had a gastric ulcer. The distribution of ulcer type in the medical group was 44·0 per cent duodenal and 56·0 per cent gastric.

The proportion of patients reporting no complaints was significantly higher among the patients who had emergency or elective PGV than in medically treated patients ($P = 0·0003$) (*Table 2*). Vagotomized patients reported less abdominal pain at any location ($P = 0·0001$), fewer dyspeptic complaints lasting for more than 1 week ($P = 0·05$), less heartburn ($P < 0·0001$) and regurgitation ($P < 0·0001$), and fewer ulcer recurrences ($P = 0·05$) compared with medically treated patients. The proportion of vagotomized patients with no complaints or those with dyspeptic complaints were not significantly different from the proportion of subjects reporting no complaints or dyspeptic complaints in the community population ($P = 0·2$ and $P = 0·9$ respectively).

Approximately 40 per cent of patients with ulceration and healthy controls reported that they had suffered abdominal complaints lasting for more than 1 week. *Table 3* shows no significant differences between controls and patients with ulceration in how often these complaints were experienced.

A significantly higher proportion of medicated patients reported that abdominal complaints had some negative impact on their working capacity compared with surgically treated patients and controls ($P = 0·002$ and $P < 0·0001$ respectively) (*Table 4*). The proportion of electively vagotomized patients reporting complaints with significant impact on working capacity was greater than that in controls ($P = 0·005$). There was no difference between controls and patients having emergency PGV in the reported influence of abdominal complaints on working capacity ($P = 0·65$).

Patients who had medical treatment reported the use of antacids, H_2-receptor antagonists and proton pump inhibitors more frequently than vagotomized patients ($P < 0·0001$). Those who had emergency or elective PGV did not use these drugs significantly more than community controls ($P = 0·66$ and $P = 0·09$ respectively) (*Table 5*).

Discussion

Comparison of dyspeptic and abdominal complaints or symptoms among surgically and medically treated patients with peptic ulceration who have not had *H. pylori* eradication therapy is apparently of only historical interest. However, when incorporating community controls without known peptic ulceration, this comparison raises some questions that are also pertinent for the evaluation of other peptic ulcer treatment regimens. It illustrates the importance of relating clinical outcome in the evaluation of different treatment modalities to the prevalence of similar complaints in the population, and is also important when assessing which dyspeptic symptoms can be ascribed to peptic ulcer disease.

The most substantial finding in this study was the lack of difference in reported abdominal and dyspeptic complaints between vagotomized patients and healthy control subjects, and that surgically treated patients had fewer of such complaints than medically treated counterparts in this long-term follow-up.

It is commonly assumed that groups of surgically or medically treated patients with peptic ulcers represent a different spectrum of the disease and therefore should not be compared. On the other hand, comparison of different treatment regimens for the same disease might give valuable information, especially when, as in this case, a healthy population was incorporated. In this study, all patients with peptic ulceration treated medically were living in Tromsø and were treated according to the treatment regimens of Tromsø University Hospital. Medical therapy for peptic ulcers was standardized and H_2 blockers could be prescribed only by specialists on the first occasion. During relapses, patients might have been offered different regimens, but regardless of differences they represent the average clinical outcome of medically treated patients for that period. Similarly, vagotomized patients may have differences in the completeness of the PGV operation, but the group represents the average clinical outcome of the surgical treatment offered for peptic ulcer disease. Comparison of the two treatment strategies should therefore be of major clinical interest.

Among healthy community controls, responders might be more likely to be subjects with abdominal complaints. This selection bias could also be true for patients with peptic ulceration. However, nothing is known about the non-responders in this study regarding dyspeptic symptoms, although the prevalence of reported complaints in responders corresponds well to that in other population-based studies in the region[10,15–17].

With abdominal complaints, it is of major importance that qualitatively similar complaints are being compared. The frequencies of reported complaints and influence on working capacity (*Tables 3* and *4*) indicate that the complaints were comparable in all four populations regarding these qualitative aspects.

In this study the definition of dyspepsia used was that recommended by an international working group[12], which distinguished it from abdominal complaints because of its high prevalence and the heterogeneous nature of abdominal symptoms. Dyspeptic symptoms with this definition are still non-specific with respect to any underlying organic disease. The probability that dyspeptic complaints in patients with previously diagnosed peptic ulceration would represent organic disease is higher than in dyspeptic controls. Comparison of dyspeptic complaints between the three ulcer populations and controls must therefore be made with caution and with such reservation in mind.

With regard to abdominal and dyspeptic complaints, Muller *et al*[9]. found an almost identical Visick grade pattern, except for grade IV, 5 years after operation in patients having PGV and blood donors serving as healthy controls. When comparing abdominal and dyspeptic complaints, the present results confirm these similarities after more than 10 years of follow-up.

Of medically treated patients 25·4 per cent reported no abdominal or dyspeptic complaints. This is in agreement with Petersen *et al.*[8], who found that 28 per cent of medically treated patients had no complaints after the initial ulcer treatment with a similar follow-up time to that in the present study. The difference in length of follow-up between medically and surgically treated patients was minimal in this study and cannot explain the reported differences in abdominal and dyspeptic complaints.

A significantly higher proportion of patients who had medical treatment found that abdominal complaints had a negative impact on quality of life compared with vagotomized patients and controls. In another study 56 per cent of patients not undergoing operation claimed that abdominal symptoms had a negative impact on some aspects of life[8]. This is in accordance with the results of the present study (47·5 per cent, data not shown), and indicates that intermittent medical treatment with antisecretory drugs had insufficient effect on the symptomatic course of peptic ulcer disease. This is also supported by the significantly higher proportion of medical patients reporting reduced working capacity due to abdominal complaints compared with both surgically treated patients and controls.

The ulcer recurrence rate, based on information from the medical records of all patients having elective PGV at Tromsø University Hospital, was 8·7 per cent with follow-up of 1–17 years after operation[18]. Reported ulcer recurrence rates after surgical treatment for peptic ulceration vary in the literature, from below 10 per cent to over 40 per cent, depending on factors such as the surgeon's experience, type of vagotomy, site of the ulcer, length of follow-up, symptomatic or total recurrences, or time intervals of endoscopic investigations[3–6,19–26].

Antisecretory medication does not eradicate *H. pylori* infection and patients with ulcers who receive medical therapy therefore have an increased risk of ulcer recurrence and dyspeptic symptoms. Nor does vagotomy eradicate *H. pylori* from the gastric mucosa[27,28]. However, the reduced acid output and/or gastric sensory denervation following vagotomy does to some extent prevent symptomatic ulcer recurrence and reduce abdominal complaints better than medical suppression therapy alone[3,4].

The self-reported ulcer recurrence rate among medically treated patients in the present study is low compared with that in other reports[8,29–31]. Again, the recurrence rate in retrospective studies is biased by such factors as negative and false-positive reporting, maintenance treatment, frequency of endoscopic examinations, systematic control regimens or symptomatic recurrences, or length of follow-up.

In the few prospective randomized studies that compare PGV and medical treatment (cimetidine maintenance therapy) of duodenal ulcers, a significantly lower recurrence rate occurred in surgically treated patients[3,4,6]. The self-assessed ulcer recurrence rates in this questionnaire study are in accordance with these previous reports.

In conclusion, this questionnaire survey revealed that abdominal and dyspeptic complaints are common in the community population. The prevalence of such complaints was similar in patients with peptic ulcers who had had vagotomy and in community controls. The study also showed that surgically treated patients reported fewer abdominal and dyspeptic complaints than did patients with ulcer who received medical treatment only.

Even though minimally invasive techniques have been developed for PGV[32], the final requiem has been held for vagotomy as elective treatment for peptic ulceration[33]. However, those who would like to make patients with peptic ulcer disease healthier or freer from gastrointestinal symptoms than the community population will probably be disappointed. This is particularly important to consider when eradication of *H. pylori* might cure the disease and thereby ulcer recurrence, but will not necessarily cure all abdominal or dyspeptic complaints among patients with peptic ulceration.

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Oral colonization is unlikely to play an important role in *Helicobacter pylori* infection

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Background This clinical and microbiological study investigated whether *Helicobacter pylori* colonizes the mouth *en route* to the pyloric antrum. It has been suggested that oral colonies are a source of reinfection after eradication of gastric infection.

Methods Some 208 patients attending for routine diagnostic endoscopy for dyspepsia were recruited. Before endoscopy, samples were collected of saliva, supragingival and infragingival plaque, and swabs were taken from the tongue, mouth and pharynx. At endoscopy, gastric antral biopsies were taken for the rapid urease test, culture and histological examination. Gastric and duodenal juice samples were aspirated. Restriction nuclease digestion with HaeIII was employed on all specimens from patients in whom there was evidence of the organism in the mouth.

Results *H. pylori* was observed in dental plaque in only 15 patients, all from the 116 who had evidence of the organism in the stomach. Restriction endonuclease digestion demonstrated that in 13 of the 15 patients the strains were identical in mouth and stomach.

Conclusion Oral colonization is a rare event, but does occur. Its rarity suggests that it is not an important factor in reinfection.

Helicobacter pylori is a Gram-negative, microaerophilic, curved, rod-shaped bacterium that colonizes human stomach. This colonization causes active chronic and acute gastritis[1,2], is strongly associated with chronic duodenal ulcer, and may be a risk factor for gastric cancer. Despite being one of the commonest infections in the world, the exact route of transmission is still unclear[3]. Some researchers have implicated the oral cavity[4–8] as a reservoir for systemic infection and perhaps a sanctuary where eradication therapy is ineffectual, thus leading to reinfection. Others have reported an absence of this organism from the mouth[9,10]. The aim of this study was to determine whether *H. pylori* colonizes the oral cavity and whether, if it does, the organism in the mouth is the same strain as that in the stomach.

Patients and methods

A total of 208 unselected dyspeptic patients referred for upper gastrointestinal endoscopy were recruited. Informed consent was obtained. The study was reviewed by the local ethics committee. Exclusion criteria included patients with a potential infection risk, a history of bleeding tendency, antibiotic therapy in the preceding 8 months and the requirement for antibiotic prophylaxis. Immediately before endoscopy, the following specimens were collected: saliva, both supragingival and subgingival plaque using a sterile periodontal curette with a gentle upward scrape against the surface of the tooth, and a swab of the tongue, mouth and pharynx. During endoscopy, specimens were collected by aspiration via a trap collector of gastric juice and (separately, in 50 subjects only) duodenal juice down to the second part of the duodenum. Three antral mucosal biopsy specimens were obtained with sterile forceps: one was used immediately for the rapid urease test, one was cultured, and the third was stored at −70°C for subsequent analysis by polymerase chain reaction (PCR) and possible restriction endonuclease digestion. Statistical analysis was by standard methods including the binomial sign test.

Specimen preparation

The dental plaque, saliva and oropharyngeal swab were vortexed in sterile solution, cultured and used for PCR. Gastric and duodenal juice specimens were initially centrifuged at high speed and the sediments tested by PCR. One gastric antral biopsy was homogenized before culture and PCR. All specimens were cultured using Colombia agar with 5 per cent horse blood and amphotericin B 10 μg/ml. *H. pylori* was identified by growth condition, typical morphology in Gram-stained preparations, a positive oxidase and a positive urease reaction.

Extraction of genomic DNA from all clinical isolates was carried out with Puregene DNA isolation kits (Gentra Systems, Minneapolis, Minnesota, USA) and applied according to the manufacturer's instructions. Two 20-base oligonucleotide primers (Oswell DNA Service, Southampton, UK) designated HP1 (5′-CTG GAG AGA CTA AGC CCT CC-3′) and HP2 (5′-ATT ACT GAC GCT GAT TGT GC-3′) were used. The primers target areas of the 16*S* ribosomal RNA gene in which there is the least sequence homology, and amplify a 109-base pair product.

PCR was performed in a 100-ml mixture containing 10 ml PCR buffer (Tris–hydrochloric acid 10 mmol/l, pH 8·3, potassium chloride 50 mmol/l), 16 μl 2′-deoxynucleotide 5′-triphosphate 200 mmol/l, 1 μl AmpErase uracil *N*-glycosylase (Perlan Elmer, Branchburg, New Jersey, USA), 1 μl AmpliTaq DNA polymerase (Amersham International, Amersham, UK), 8 μl magnesium chloride 2·0 mmol/l, 10 μl HP1 and HP2 2 mmol/l,

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and 5 μl DNA template. The mixture was made up to 100 μl by adding ultrapure water. This was then topped up with 50 μl sterile mineral oil to prevent evaporation during temperature cycling.

PCR reaction cycle

A two-step cycle was used in the automated thermocycler (Hybaid, Ashford, UK). This consisted of 40 cycles at 95°C for 30 s, 60°C for 30 s and 72°C for 30 s. The final cycle was maintained at 72°C for 5 min.

The amplified PCR products were analysed in ethidium bromide-stained agarose gel run at 8·8 V/cm for 30 min. The gel was photographed under ultraviolet light.

Restriction endonuclease

PCR products from patients in whom *H. pylori* had been detected in the mouth were digested with HaeIII (Sigma Diagnostics, Poole, UK). This was run in a water bath at 37°C for 4 h and electrophoresed in a 2 per cent agarose gel at 8·8 V/cm for 1 h.

Results

Using the criterion of culture and/or rapid urease test of the antral biopsies, 82 patients (39 per cent) were *H. pylori* positive and 115 were *H. pylori* negative (data were not available for the remaining 11 subjects). Using the criterion of PCR, the corresponding results were 116 positive and 92 negative.

No sample of gastric or duodenal juice was positive by culture or urease test. However, 36 samples (17 per cent) of gastric juice and six of 50 (12 per cent) samples of duodenal juice were positive by PCR.

With regard to the mouth, no salivary or swab sample was positive for *H. pylori* by any test. Two of 180 specimens of dental plaque were *H. pylori* positive by culture, and these two samples plus 13 more were positive by PCR. All of these 15 patients were also positive for *H. pylori* in both antral biopsy and gastric juice. Restriction endonuclease digestion of the amplified PCR product from these 15 patients showed that 13 of the dental plaque isolates had identical restriction digest patterns to those of the organisms in the stomach, whereas in the other two patients the patterns were slightly different. On the other hand, only four of the 15 patients had a similar pattern in all three sites (plaque, stomach and duodenum); in the other 11 the duodenal organisms were definitely different.

Discussion

The PCR technique seemed to be more sensitive than culture or the rapid urease test in detecting *H. pylori*[11]. The significance of this finding, which has been well reported, is not clear. It may mean, as some believe, that culture and the urease test occasionally fail to demonstrate live organisms that are present in very low numbers. However, the fact that PCR sometimes finds evidence of *H. pylori* in gastric, and even in duodenal, juice (the organism is particularly sensitive to extremes of pH[12]) suggests that the molecular technique might be demonstrating fragments of the dead organism that still contain intact the targets of the primers.

In the oral samples there was never any evidence of *H. pylori* except in plaque. In 15 of 208 plaque samples PCR was positive for the organism, but in only two of these was the PCR result accompanied by a positive culture. It is concluded that colonization of the mouth by *H. pylori* is a rather unusual event and that it does not occur except in plaque. Depending on the view taken of the relationship between PCR results and those from culture and the rapid urease test, it may also be concluded, either that the greater sensitivity of PCR is responsible for the larger score by that technique, or that the culture gives the true picture of present colonization whereas the PCR is evidence of (recent) past colonization. At present, it is not possible to choose between these interpretations.

Whatever interpretation of the oral findings is chosen, the fact remains that, of 116 patients with evidence from PCR of *H. pylori* in the stomach, 15 were also positive in the mouth; by contrast, of 92 patients with no trace of the organism in the stomach, none showed evidence of *H. pylori* in the mouth. This asymmetrical distribution of the 15 patients is highly significant ($P < 0.0002$, binomial sign test). In other words, colonization in the mouth is linked with colonization in the stomach. This finding is further supported by the restriction endonuclease digestion studies.

As already noted, some observers have reported that they could not find *H. pylori* in the mouth, whereas others have confirmed its presence. Possible reasons for these discrepancies include the small numbers of patients studied, differences in population prevalence, and the difficulty of culturing this fastidious micro-organism from the oral cavity with its complex and varied normal flora. Even in the present study, positive cultures were obtained from plaque in only two of the 116 subjects who were PCR positive in the stomach. Clearly this small number is not significantly different from the zero score in the plaque in the 92 PCR-negative subjects. However, the present study provides the largest number of data of all published papers on the detection of *H. pylori* in the oral cavity, and the use of PCR and restriction endonuclease digestion was crucial in establishing the link between mouth and stomach.

It is concluded that *H. pylori* sometimes colonizes dental plaque, but it would appear that such colonization is transient. The hypothesis that the mouth is a sanctuary in which the organism can survive the attack of antibiotics and later produce reinfection gains little support from these data.

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Surgical Infection Society of Europe Abstracts

The following abstracts and posters were presented at the 11th annual meeting of the Surgical Infection Society of Europe held in London on 15–16 May 1998.

Abstracts of papers

Endotoxin tolerance induces enhancement of phagocytic activity of mononuclear cells in a porcine endotoxin shock model

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Background Endotoxin (ET) tolerance represents a non-specific refractoriness to ET as an essential protective mechanism in the early phase of infection to prevent unreasonable expansion of the inflammatory immune response. Its exact biological basis remains unclear, besides a well known downregulation of pro-inflammatory mediators in endotoxaemia. The aim of the present study was a quantitative *in vitro* evaluation of mononuclear phagocytic activity in ET shock.

Methods Seven pigs were immunized over 5 days by increasing doses of atoxic ET from *Rhodopseudomonas sphaeroides* (group T) and compared with six control animals (group C) before induction of an ET shock with a continuous ET challenge of *Salmonella friedenau* at 250 ng kg^{-1} h^{-1}. Phagocytosis was measured by flow cytometry, demonstrating ingestion of opsonized fluorescent *Escherichia coli*. A commercial test kit (Phagotest; Orpegen, Heidelberg, Germany) was used for the tests.

Results

	Immunization period (days)					ET shock (h)				
	1	2	3	4	5	1	3	6	9	12
C	679	715	631	670	—	459	723	554	210	—
T	532	639	529	438	—	294	683	617	743	703

Values are fluorescence intensity units

Conclusion The functional assessment of mononuclear cells of ET-tolerant animals revealed an increase in phagocytic activity compared with control animals which resulted in a significantly higher survival rate ($P = 0·05$).

Heparin and enoxaparin enhance endotoxin-induced tumour necrosis factor α production in human monocytes

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Background The ability of heparin to bind antithrombin III and to inhibit the coagulation cascade is widely used in clinical practice. Heparin has other potentially important properties, such as binding to various proteins (e.g. fibronectin, heparin binding protein or chemokines) or to leucocyte receptors (e.g. selectins) and could be used as a pleiotropic immunomodulator. It was hypothesized that heparin and enoxaparin (low molecular weight heparin) would alter the effect of another potent immunomodulator, endotoxin (lipopolysaccharide; LPS), which induces release of tumour necrosis factor (TNF) α from monocytes.

Methods Monocytes from five healthy donors were isolated by density gradient centrifugation and stimulated for 24 h with heparin 0·1–1000 μg ml^{-1}, enoxaparin 0·1–1000 μg ml^{-1} and LPS 10 ng ml^{-1}. Monoclonal anti-CD14 antibody (MY4 10 μg ml^{-1} or isotype-matched immunoglobulin G control was used to assess the role of CD14 blockade. TNF-α release was measured by enzyme-linked immunosorbent assay.

Results Initial dose–response studies demonstrated that heparin at more than 10 μg ml^{-1} and enoxaparin 1000 μg ml^{-1} significantly increased LPS-induced TNF-α release. Subsequent blocking studies confirmed that heparin is more potent than enoxaparin in enhancing LPS-induced TNF-α release. Blockade of CD14 inhibited the effect of LPS as well as the effect of heparin and enoxaparin in enhancing LPS-induced TNF-α release.

Conclusion Heparin and enoxaparin enhance LPS-induced TNF-α release from isolated monocytes. This immunomodulatory effect is stronger for heparin than for enoxaparin and may be biologically important in patients with sepsis with increased LPS levels. Binding of LPS to CD14 on monocytes is the important initial mechanism to induce TNF-α release from monocytes, because blockade of CD14 inhibited both the effect of LPS and the enhancing effect of heparin and enoxaparin.

Postoperative wound infection rate after hernia repair: a European study

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Background This was a prospective controlled study of wound infection after hernia repair in five European countries: Spain, Hungary, Germany, Italy and Turkey.

Methods The period of the study was from 1 February to 30 April 1996 and included patients aged 18 years or more. The study determined wound infection rates in all abdominal wall and incisional hernia repair surgery and established the value of antibiotic prophylaxis in cases of hernia repair with a mesh. In these cases, cephazolin, in a single 1-g dose, was administered during induction of anaesthesia. For analysis the computer program 'Surgery' was used. Some 229 surgical patients were included of mean age 55·9 years; 76·9 per cent were male and 23·1 per cent female. In all, 213 patients were submitted to elective surgery and 16 to emergency operation. There were three epigastric hernias, 16 umbilical, seven femoral, 159 inguinal, 40 incisional and four others.

Results Sixteen (7·0 per cent) patients developed postoperative wound infections: ten superficial and six deep. Fifteen (6·9 per cent) of the 216 patients submitted to clean surgery developed wound infections, and one of 11 who had clean-contaminated surgery. There were no statistical differences between staff surgeons and residents. In 107 patients the duration of operation was less than 1 h and the rate of wound infection was 5·6 per cent; in 93, the duration was between 1 and 2 h and the infection rate was 7·5 per cent; and in 24 the duration was over 2 h and three patients developed a wound infection. The greatest rate of wound infection occurred in umbilical hernias (two of 16); the rate was 6·9 per cent for inguinal and two of 40 for incisional hernia repair. In 20 patients a mesh was placed and antibiotic prophylaxis was used; one of these 20 patients developed a wound infection compared with 7·2 per cent of 209 patients in whom hernia repair was done without a mesh. Thirty patients received antibiotic prophylaxis, of whom two developed wound infections; of the 199 patients who did not receive antibiotic prophylaxis 14 (7·0 per cent) developed wound infections. The mean duration of the postoperative period was 5·3 days in patients without wound infection and 6·3 days in patients with infections; there were no deaths.

Prospective randomized double-blind clinical study of perioperative immunonutrition

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Background It has been shown that perioperative immunonutrition upregulates the immune response, improves gut oxygen metabolism and modulates the inflammatory response after surgery. This trial evaluated the use of perioperative immunonutrition to improve outcome after major abdominal operations.
Methods Some 206 patients with gastric, pancreatic or colorectal cancer were randomized in a double-blind fashion to receive either a formula enriched with arginine, ω-3 fatty acids and RNA (group E; $n = 102$) or a control isonitrogenous, isocaloric, enteral diet (group C; $n = 104$). Seven days before surgery the patients drank 1 litre per day of either the control or enriched diet. Postoperative jejunal infusion with the same diet began 6 h after surgery and continued for 7 days after operation. Twenty patients were withdrawn from the study; six were not compliant with the preoperative diet and 14 underwent palliative surgery for intraoperative evidence of metastatic disease.
Results The two groups were comparable for preoperative, age, sex, weight, Karnofsky index, nutritional parameters, haemoglobin, type and duration of surgery, blood loss and rate of transfusion. Fifteen of the 186 patients who underwent curative surgery had an anastomotic dehiscence (five in the enriched group, ten in the control group). Some 171 patients were valid for evaluation (85 in group E and 86 in group C). There were no deaths in group E and one patient died in group C (P not significant). The rate of postoperative infection was 11 per cent (nine of 85 patients) in group E and 26 per cent (22 of 86) in group C ($P = 0·004$). Mean(s.d.) duration of antibiotic therapy was 6·7(1·2) days in group E and 9·1(2·5) days in group C ($P = 0·001$). Length of hospital stay was 11·1(4·4) days in group E and 12·9(4·6) days in group C ($P = 0·01$).
Conclusion Perioperative immunonutrition improved outcome in patients with cancer undergoing major surgery.

The battle against methicillin-resistant *Staphylococcus aureus*: 'search and destroy' can work in a high-prevalence region

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Background In the Netherlands, the proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) among *S. aureus* isolates is low (1·5 per cent) despite an increase in neighbouring countries during the past decade. Since 1989 a nationwide guideline has been followed, which is based on the principles of 'search and destroy'. The mainstay of this guideline is that patients who potentially carry MRSA, predominantly those who are transferred from foreign countries, are strictly isolated in a single room with hospital staff wearing a mask, cap, gown and gloves. Screening cultures are taken from the nose, throat, perineum, skin lesions and wounds (sputum if present and urine in the event of a catheter) of these patients, and interventions such as surgery are postponed, whenever possible, until the results of cultures are known. This guideline is criticized because of its failure rate and high costs.
Methods From a 5-year retrospective survey this guideline has been evaluated.
Results Between January 1992 and September 1997, 1803 samples were taken from 363 patients for screening of MRSA. In 355 patients, who appeared to be MRSA negative, a total of 1459 cultures was taken, mean 4 (range 4–76) cultures, whereas in eight patients who appeared to be MRSA positive a total of 344 cultures was taken, mean 43 (range 4–169) cultures. Some 165 (45 per cent) were surgical patients; 25 per cent of the patients were treated in the outpatient clinic. The eight MRSA-positive patients (trauma four, respiratory insufficiency two, cerebral haemorrhage one, urological disorder one) had to be treated clinically with vancomycin. All of these patients were transferred from a hospital in a foreign country and fulfilled the criteria for MRSA screening according to the guideline. In this 5-year period, no culture from other hospital patients revealed MRSA. The cost for MRSA-negative patients was $36 000. The costs of cultures, preventive measures and antibiotic treatment in the eight MRSA-positive patients were more than twice as high.
Conclusion The prevalence of MRSA in a Dutch university hospital is low. A nationwide guideline of 'search and destroy' in a European region of high MRSA prevalence is highly effective and seems to be cost saving. Screening programmes for MRSA would benefit from identification of so-called MRSA-free hospitals.

Sex and genetics as new determinants in sepsis

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Background The prognosis of sepsis has been found to be genetically determined, with a high mortality rate in patients who are homozygous for the tumour necrosis factor (TNF) B2 allele. In animal studies sex differences relate to hormonal and immunological changes which are associated with an increased susceptibility to sepsis in males.
Methods The prognostic value of sex and genetic determination was evaluated in 51 patients (19 women) with surgical sepsis. In a subgroup of patients ($n = 18$) TNF gene polymorphism was determined in relation to sex. There were no differences between the men and women with respect to age (mean age 56 years for women, 53 years for men), and cause and severity of sepsis. The predominant causes of sepsis were peritonitis and necrotizing pancreatitis.
Results The prognosis of sepsis was significantly different in women compared with men. Twenty-four of 33 men and five of 19 women died in hospital ($P < 0·01$, log rank test). Some 40 per cent of patients who were homozygous for the *TNFB2* allele died while one-third of patients who were heterozygous (*TNFB1/TNFB2*) survived. Of 12 men in whom genomic polymorphism was studied, seven died. Six of these non-survivors were homozygous for the *TNFB2* allele. Both female patients who died were homozygous as well.
Conclusion Sex differences could be confirmed in human sepsis with a significantly improved prognosis for women. Genetic determination in female and male patients homozygous for *TNFB2* was associated with poor prognosis. Because of their prognostic importance, sex and genetic screening should be regarded as important determinants in further sepsis studies.

Intestinal intramucosal pH is the pivotal indicator of mucosal damage in goal-directed therapy of endotoxin shock

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Background 'Goal-directed' therapy of patients with septic shock has been frequently advocated to avoid end-organ damage and has been focused at haemodynamic parameters and variables of oxygen transport. More recently intramucosal pH (pH_i) obtained by tonometry has been introduced but its value as an indicator of mucosal integrity in septic shock is uncertain.
Methods Nineteen pigs were infused with $250\,\mu g\,kg^{-1}$ *Escherichia coli* endotoxin over 30 min and thereafter subjected to fluid resuscitation to maintain postcapillary wedge pressure at pre-endotoxin levels. Four animals received fluid only while three groups of five animals each underwent additional catecholamine therapy either to maintain mean arterial pressure (MAP) above 70 mmHg by individual doses of adrenaline (group

E) or noradrenaline (group NE) or to increase cardiac output (CO) by a constant infusion of dopexamine 7 µg kg^{-1} (group DX). After induction of anaesthesia, catheters were introduced into the carotid artery and jugular vein for haemodynamic measurements, and drug and fluid delivery. CO was obtained using a thermodilution artery and the portal vein, and a catheter was inserted into the portal vein. The pH$_i$ was obtained by a tonometer balloon in the sigmoid. Animals underwent therapy for 4 h. At the end of the experiment specimens of ileal and colonic mucosa were taken, processed and subjected to morphometry after haematoxylin and eosin staining. Damage to the mucosa was defined as disruption of the epithelial layer and was documented as a percentage of the investigated surface.

Results Therapy led to a maintenance of MAP above 70 mmHg at 4 h in groups E and NE. CO was significantly increased to a mean(s.d.) of 137(7) per cent in groups E, NE and DX at 4 h. pH$_i$ was decreased in all groups by 3·5–9·4 per cent. Mean mucosal damage ranged from 4 to 46 per cent depending on the group. Regression analysis of the impact of the variables MAP, CO, arterial oxygen content, mixed venous saturation and pH$_i$ at 4 h on percentage of ileal mucosal damage showed significance only for pH$_i$ ($r = -1{\cdot}1$, $P = 0{\cdot}01$). When the relative drop of pH$_i$ from baseline to 4 h was introduced as a variable, significance was established also for damage to the colonic mucosa ($r = 0{\cdot}67$, $P < 0{\cdot}05$).

Conclusion pH$_i$ is the pivotal independent indicator of damage regarding disruption of the intestinal mucosa and potential sequelae in endotoxin-induced shock. Therefore maintenance or improvement of pH$_i$ should be given priority over other therapeutic goals.

Production of interleukin 6 and monocyte chemoattractant protein by the human peritoneum during abdominal surgery *in vivo* and *in vitro*

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Background Major abdominal operations as well as peritonitis lead to an increase of various cytokine concentrations in plasma. The peritoneum is a potential source of cytokines. The production of interleukin (IL) 6 and monocyte chemoattractant protein (MCP) 1 by the peritoneum *in vivo* during elective major abdominal operations was investigated. In addition the reaction of the peritoneum to bacteria or lipopolysaccharide (LPS) was tested *in vitro*.

Methods A small chamber (inner volume 500 µl) was fastened to the patient's parietal peritoneum, covering an area of 3·1 cm^2. During the operation (at least 5 h), the chamber was perfused with buffered electrolyte solution (2 ml h^{-1}) and the perfusate was collected hourly. For *in vitro* culture, a small piece (10 cm^2) of the peritoneum was excised, placed across the wells of a microtitre plate, fixed by means of the plate cover and subsequently incubated with culture medium containing LPS or whole bacteria (*Escherichia coli*) for 5 h. The culture supernatants and perfusate samples were assayed for IL-6 and MCP-1 concentrations by enzyme-linked immunosorbent assay.

Results Production of IL-6 and MCP-1 started within the first hour. IL-6 was released thereafter constantly (mean(s.d.) 90(50) pg cm^{-2} h^{-1}) during the whole of the procedure. MCP-1 secretion increased from 66(26) pg cm^{-2} during the second hour to 237(199) pg cm^{-2} during the fifth hour. Peritoneum cultured with LPS or bacteria released amounts of IL-6 and MCP-1 that were significantly higher (6175(3515) and 3758(2457) pg cm^{-2} h^{-1}) than those of the corresponding control samples.

Conclusion The peritoneum reacts to surgical procedures with production of IL-6 and MCP-1. These are mediators that participate in the initiation of an inflammatory process. Moreover, it is able to upregulate its mediator production in the presence of Gram-negative bacteria or LPS. Modulation of the cytokine production of the peritoneum may offer treatment options for inflammatory processes in the abdomen.

Nitric oxide production mediates cytokine-induced inhibition of hepatocyte gluconeogenesis and protein synthesis

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Background Cytokines are thought to play an important role in the hepatocellular dysfunction that occurs during sepsis, and they have been implicated in the regulation of the nutritional state. The signal transduction mechanisms by which cytokines exert their effects have not been elucidated fully. Several studies have shown that nitric oxide is produced in large amounts *in vitro* by hepatocytes following exposure to septic stimuli. The aim of this study was to investigate a possible mediation by nitric oxide and guanosine 3′,5′-cyclic monophosphate (cGMP) of the effect of cytokines on gluconeogenesis and protein synthesis by isolated rat hepatocytes.

Methods Cells were isolated by the collagenase perfusion method and cultured for 24 h before making the following additions: tumour necrosis factor (TNF) α, interleukin (IL) 1, the nitric oxide donor morpholinosydnonimine (SIN-1), *N*-nitro-L-arginine (NAME), aminoguanidine (AG), 8-bromo-cGMP, methylene blue and combinations thereof. After that, cells were cultured for another 60 min or 24 h. Protein synthesis was determined as the incorporation of [^{14}C]leucine in proteins, and gluconeogenesis as the glucose production from [^{14}C]alanine.

Results Both TNF-α and IL-1 decreased the [^{14}C]leucine incorporation into proteins (mean(s.d.) 1·60(0·12) and 1·00(0·09) *versus* 2·95(0·13) nmol per 10^5 cells per 60 min for TNF-α and IL-1 respectively *versus* controls; $n = 11$, $P < 0{\cdot}01$) and the synthesis of glucose (10·81(0·94) and 10·87(1·44) *versus* 14·50(1·50) nmol per 10^5 cells per 24 h; $n = 11$, $P < 0{\cdot}05$), which were also diminished by SIN-1 (0·79(0·09) *versus* 2·95(0·13) nmol per 10^5 cells per 60 min and 8·46(1·30) *versus* 14·50(1·50) nmol per 10^5 cells per 24 h respectively; $n = 11$, both $P < 0{\cdot}01$). The cytokine effect was accompanied by an increase in nitric oxide synthesis (199·1(6·9) and 214·7(9·2) *versus* 134·4(7·4) pmol per 10^5 cells per 24 h for TNF-α and IL-1 respectively *versus* controls; $n = 11$, both $P < 0{\cdot}01$) and cGMP (0·95(0·14) and 0·96(0·11) *versus* 0·56(0·04) pmol per 10^5 cells per 24 h; $n = 11$, $P < 0{\cdot}01$) and lipid hydroperoxide (1·97(0·14) and 2·02(0·15) *versus* 1·12(0·07) nmol per 10^5 cells per 24 h; $n = 11$, $P < 0{\cdot}01$) cell content. Both NAME and AG were able to reverse all these effects.

Conclusion The generation of nitric oxide may mediate the inhibition of protein synthesis and gluconeogenesis caused by cytokines in rat hepatocytes.

The surgeon's impact on the abdominal compartment in abdominal sepsis

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Background Rapid and efficient surgical management of abdominal sepsis is known to be critical for outcome in peritonitis. Little, however, is known about the impact of surgery on the pathophysiological environment in the abdominal cavity or whether cytokines can be washed out.

Methods In 19 patients with diffuse peritonitis intra-abdominal cytokines (interleukin (IL) 6 and IL-8), phagocyte lysosomal enzymes (elastase, cathepsin B, myeloperoxidase) and functional enzymes (opsonins, antithrombin III (AT-III)) were followed during and after operation (48 h). A second group of 13 patients underwent staged laparotomy. In these patients the same variables were examined and compared.

Results Lysosomal enzymes as well as cytokine levels were raised about 1000-fold in the initial peritonitis exudates. Intra-abdominal lavage resulted in a profound but very short-lasting reduction of these parameters. By 2 h later, concentrations were back to almost the original values and then decreased slowly over 2 days,

but only when surgery was successful. The same pattern was found in purulent exudates drawn in etappenlavage operations. The levels of the above variables stayed high until obvious clearance of the abdominal cavity was obtained. The concentration of opsonins and AT-III in peritoneal exudates was about 60 per cent that of patients' sera but in purulent exudates a distinct deficit in protein function was found. Only in clear exudates did protein activity match the protein concentration.
Conclusion Surgery in peritonitis resulted in a very short-lasting washout of mediators of inflammation followed by a profound relapse. A slow decrease of these parameters could be observed after 48 h if the source of the peritonitis had been eradicated. It is concluded that the main benefit of staged laparotomy is the supervision of source control rather than the effect of lavage.

Translocation of bacteria and endotoxin to mesenteric lymph nodes and the inflammatory consequences

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Background Translocation of intestinal bacteria to mesenteric lymph nodes (MLNs) has been documented in humans in a variety of circumstances, yet its clinical significance remains to be established. Depending on the underlying disease, reported translocation rates range between 0 and 70 per cent. To correlate translocation with local and systemic responses, the translocation of bacteria and endotoxin to MLNs, the inflammatory response within the MLNs and respective systemic effects were investigated in a series of patients with carcinoma of the caecal region.
Methods Two lymph nodes were removed from the right colonic mesentery of each patient before resection. The presence of bacteria in the lymphatic tissue was determined by either bacteriological culture methods or DNA preparation (polymerase chain reaction (PCR)). Determination of local and systemic inflammatory responses was performed by analysis of inflammatory mediators in plasma and MLN supernatants, and by immunohistochemistry.
Results Living bacteria (mostly staphylococci) were detected by culture methods in seven of the ten patients and in nine of 20 lymph nodes. PCR revealed traces of Enterobacteriaceae in four of ten patients and in six of 20 MLNs. There was no detectable bacteraemia. Endotoxin (more than 0·1 pg ml^{-1}) was found in the plasma of seven patients (median 0·65 pg ml^{-1}) and in nine MLNs (median 7 pg per 25 mg) of five patients. Only in four patients was endotoxin detected simultaneously in MLNs and plasma. Gram-negative MLN cultures correlated with endotoxin concentrations in MLN homogenates. However, bacteriological data and endotoxin concentrations did not correspond to local or systemic concentrations of inflammatory mediators (tumour necrosis factor α, interleukin (IL) 6, IL-8, IL-10, CD14).
Conclusion From these results it may be concluded that translocation of bacteria and endotoxin to the MLN level occurs in a large majority of patients with caecal carcinoma. This, however, may be without clinical significance since detectable inflammatory reactions did not correspond to the degree of translocation, neither at the local nor at the systemic level. Additionally, there may be considerable variations in inflammatory reactions and the extent of contamination by bacteria and endotoxin between different lymph nodes from a single patient.

Control of the use of prophylactic antibiotics in surgery in Belgium

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Background The prophylactic use of antimicrobial agents in surgery is widespread practice. Different scientific organizations have published guidelines for the prophylactic use of antibiotics. Recently the degree of adherence to guidelines and real practice was studied in Belgium. In 11·4 per cent of the operations for which prophylaxis is indicated, it was not given. Prophylaxis was given in 55·6 per cent of the operations in which it was not indicated; 15 per cent of courses exceeded 2 days. To stimulate the use of guidelines and control the dispensing, a budget based on surgical intervention was introduced.
Methods A multidisciplinary group of experts, using leading guidelines, indicated for all surgical interventions the theoretical need for antimicrobials and the best choice of product(s). In Belgium, antimicrobials used in hospitals are reimbursable. Patient-based hospital listings, describing details of surgical interventions and drugs administered, must be sent to the paying insurance company. The price setting of reimbursable drugs is the responsibility of the Ministry of Economic Affairs. As a consequence, the price is fixed. Using the list compiled by the multidisciplinary group, administrators calculated, for each intervention, the amount of money necessary for appropriate prophylaxis.
Results It was decided to finance hospitals for the antimicrobial prophylaxis using a fixed budget linked to the surgical intervention. For registration reasons, it was decided to divide the total budget to a first fixed 75 per cent of the budget linked to the surgical fee and to a second part being 25 per cent of the reimbursable price of all antimicrobials given during a 3-day perioperative period.
Conclusion This strategy was introduced by law in Belgium in May 1997. Many local working groups discussed thoroughly the introduction of this new strategy. To optimize further the rules and the application, a national working group was set up. In many hospitals, guidelines on the prophylactic use of antimicrobial agents have been updated. In general, many hospital pharmacists observe an important reduction in prophylactic antimicrobial use. No data are available concerning the probable improvement in quality.

Prognostic peritonitis model: validation of a score based on control of an infective focus in patients with postoperative peritonitis

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Background Severe cases of peritonitis have a high associated mortality rate. In terms of decreasing resources there is an urgent need to identify patients at high risk for complications. None of the common scoring systems includes information on intraoperative control of the septic focus, although this is considered the most important single factor for outcome prediction. The peritonitis prediction model (PPM) identified patients at risk more accurately than other scores. The score was validated by applying it to a cohort of patients with postoperative peritonitis and at high risk for postoperative complications.
Methods From October 1994 to October 1997 patients with postoperative peritonitis were followed prospectively. Abscesses were included when open surgical drainage was necessary. Besides demographic data, details of underlying disease, concomitant disease, preoperative duration of symptoms, source of peritonitis, bacteriology, mode of repair, preoperative and postoperative organ failure, septic and non-septic complications, and circumstances of death were recorded. Score values were calculated from the data using the PPM method (Acute Physiology Score + 1/2 age + 3 × number of concurrent diseases + 25 (if infective focus unresolved) + 3 × Goris Multiple Organ Dysfunction score on postoperative day 1).
Results There were 55 patients with peritonitis, of whom 16 died. With the cut-off point of a score of less than 55 points, only one of 24 patients died in the low-risk group and 15 of 31 in the high-risk group. In contrast, when Acute Physiology And Chronic Health Evaluation (APACHE) II was used, with a cut-off point of below 10 points, three of 24 patients in the low-risk group died and 18 of 31 patients in the high-risk group survived. There was only one patient with an uncontrolled infective focus in the low-risk group as defined by PPM while there were eight of these in the low-risk group for APACHE II. In the low-risk group after

PPM there were 0·18 infectious complications per patient and in the high-risk group the mean was 1·1. In groups identified by APACHE score the values were 0·44 and 0·93.
Conclusion Postoperative peritonitis is one of the most lethal complications in abdominal surgery. The PPM is able reliably to identify patients at low risk for complications, thus focusing attention on a subgroup of patients with a 50 per cent risk of fatal outcome. Postoperative infectious complications are predicted as well for the high-risk group. The accuracy of PPM is superior to that of APACHE II.

Contribution of leptin to the metabolic response to sepsis

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Background Leptin, a protein secreted by adipose tissue, has metabolic effects similar to sepsis, producing an increase in resting energy expenditure (REE) and anorexia. Since leptin secretion has been shown recently to be induced by endotoxin the authors have examined whether the metabolic effects of sepsis might be attributable to increased plasma leptin concentration.
Methods Twenty adult patients with abdominal sepsis (sepsis score 10–27, median 16) were studied within 96 h of admission and compared with 20 healthy control subjects. Fasting REE and plasma insulin, cortisol and leptin concentration were measured by indirect calorimetry and radioimmunoassay respectively. Fat mass (FM) was measured by anthropometry.
Results REE, FM and cortisol concentration were significantly greater in patients with sepsis than healthy controls but fasting plasma insulin and leptin concentrations were not.

	Control	Septic
REE (kcal kg FFM^{-1} day^{-1})	30·2(4·3)	36·0(7·2)*
FM (kg)	15·5(9·4)	23·4(4·2)*
Insulin (μunits ml^{-1})	6·6(2·9)	8·4(5·3)
Cortisol (μmol l^{-1})	250(151)	540(172)*
Leptin (ng ml^{-1})	7·0(5·2)	6·9(6·1)

Values are mean(s.d.). *$P < 0{\cdot}01$.

Leptin concentration correlated significantly with FM in controls ($r = 0{\cdot}78$, $P < 0{\cdot}001$) and patients with sepsis ($r = 0{\cdot}74$, $P < 0{\cdot}001$), but the slope of the line relating the variables was significantly lower in sepsis ($F = 1{\cdot}62$, $t = 2{\cdot}34$, $P < 0{\cdot}05$). Leptin concentration also correlated significantly with fasting plasma insulin concentration in controls ($r = 0{\cdot}67$, $P < 0{\cdot}001$) and patients with sepsis ($r = 0{\cdot}55$, $P < 0{\cdot}05$).
Conclusion Sepsis is not associated with increased plasma leptin concentration, either in absolute terms or relative to FM. Leptin is unlikely to play a primary role in the metabolic effects of human sepsis.

Cytokine production by human peritoneal mesothelial cells

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Background It has been demonstrated previously that monolayers of human peritoneal mesothelial cells (HPMCs) are able to release various cytokines after stimulation with heat-killed micro-organisms, suggesting that these cells play an active role in abdominal inflammatory reactions. In a normal setting, HPMCs are in contact or in close vicinity with other cell types (macrophages, fibroblasts, lymphocytes, other white blood cells) which also release inflammatory mediators when they are activated. This study determined the effect of these mediators on the response of HPMCs to heat-killed *Escherichia coli* and an attempt was made to modulate this reaction.
Methods Monolayers of confluent HPMCs were incubated with various compounds and stimulated with heat-killed *E. coli*. Some 24 h later, the concentration of interleukin (IL) 6, IL-8, RANTES and monocyte chemoattractant protein (MCP) 1 was measured in the supernatants by enzyme-linked immunosorbent assay.
Results

	Cytokine production			
	IL-6	IL-8	RANTES	MCP-1
TNF-α (0·1–1·0 ng ml^{-1})	↑a	↑a	↑s	↑a
IFN-α (1 × 10^3 units ml^{-1})	↑a	0	↑s	↑a
IFN-γ (1 × 10^3 units ml^{-1})	↑	0	↑s	↑a
IL-10 (500 ng ml^{-1})	0	0	0	0
Indomethacin (0·1–5 μg ml^{-1})	0	0	0	0
Zymosan (1 mg ml^{-1})	0	0	↓	0

TNF, tumour necrosis factor; IFN interferon. ↑, Increase; ↓, decrease; a, additive effect; s, synergistic effect; 0, no effect

Conclusion These data demonstrate that the production of cytokines by HPMCs stimulated by *E. coli* may be enhanced by some mediators secreted by cells present in the abdominal cavity. They suggest that prostaglandins secreted by HPMCs do not influence the output of IL-6, IL-8, RANTES and MCP-1. Zymosan, which has a protective effect in experimental peritonitis, selectively decreases RANTES secretion. Together with the experiments conducted with interferons, this result indicates that it is theoretically possible to alter the cellular composition of an intraperitoneal inflammatory reaction. Whether this is beneficial remains to be investigated.

Bi-allelic *NcoI* polymorphism within the tumour necrosis factor locus and its association with the prognosis and outcome of patients with sepsis

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Background Tumour necrosis factor (TNF) α plays a central role in the pathophysiology of sepsis, septic shock and multiple organ failure. These host reactions are associated with increased TNF levels in the circulation, presumably due to increased TNF production.
Methods In a group of patients with sepsis, a bi-allelic *NcoI* TNF-β polymorphism was studied and correlated to TNF plasma level, TNF p55 receptor level, outcome and the incidence of multiple organ failure.
Results Patients homozygous for the allele *TNFB2* displayed higher multiple organ failure scores than heterozygous (*TNFB1*/*TNFB2*) patients.
Conclusion It remains to be elucidated in future studies whether monitoring of genetically influenced differences in cytokine gene regulation may be useful for preoperative selection or patients at high risk in septic situations for intensive monitoring or prophylactic treatment. Moreover it might be used to select patients for clinical trials utilizing anti-TNF strategies.

Postoperative fever and outcome in major surgery

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Background This study determined whether fever is a predictor of outcome after major abdominal and thoracic surgery.
Methods A retrospective chart review of 179 patients who underwent major surgery (oesophagectomy, pneumonectomy, gastrectomy or colectomy) was performed. Demographic data, the operation performed, the nature of the underlying disease, transfusion requirements, daily temperature and white cell count

on the first 7 days after operation were recorded. Fever was defined as a temperature above 38·5°C.

Of the 179 patients 53 (29·6 per cent) developed fever and 126 (70·4 per cent) did not. The mortality rate in the first group was 23 per cent (12 of 53) and in the second group 4·0 per cent (five of 126). The overall mortality rate was 9·5 per cent (17 of 179). Logistic regression analysis showed that fever on days 5, 6 and 7 after operation was an independent predictor of outcome ($P < 0{\cdot}05$, $P < 0{\cdot}05$ and $P < 0{\cdot}01$ respectively).

Results

	Deaths			
	All	No fever	Fever	P^*
Elective procedures	8 of 133 (6·0)	3 of 103 (2·9)	5 of 30 (17)	0·01
Thoracic	4 of 71 (6)	1 of 58 (2)	3 of 13 (23)	
Upper gastrointestinal	3 of 24 (12)	1 of 15 (7)	2 of 9 (22)	
Lower gastrointestinal	1 of 38 (3)	1 of 30 (3)	0 of 8 (0)	
Emergency procedures	9 of 46 (20)	2 of 23 (9)	7 of 23 (30)	n.s.
All	17 of 179 (9·5)	5 of 126 (4·0)	12 of 53 (23)	< 0·001

Values in parentheses are percentages. $^*\chi^2$ test; n.s., not significant

	Mean temperature (°C)		
	Day 5	Day 6	Day 7
Survivors	37·2	37·1	37·1
Non-survivors	37·9	38·0	38·1
P^*	< 0·005	< 0·01	< 0·005

*Mann–Whitney *U* test

The most common causes of fever were pneumonia (14 patients), organ space infection (nine), urinary tract infection (eight) and wound infection (four).

Conclusion Fever in the late postoperative course (days 5–7 after operation) is an independent predictor of outcome after major abdominal and thoracic surgery.

Effect of continuous plasma filtration coupled with sorbent absorption in a model of Gram-negative sepsis

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Background The treatment of Gram-negative sepsis is challenging. No clinical treatment has been shown to improve survival significantly. This study evaluated outcome and removal of mediators of sepsis using continuous plasma filtration (CP) coupled with sorbent absorption (SA) in a single-shot endotoxin model.

Methods New Zealand White rabbits were divided into four groups: CP only (group 1; $n = 10$); CP + endotoxin (0·05 mg per kg body-weight) (group 2; $n = 20$); CP + SA (group 3; $n = 19$); and CP + SA + endotoxin (group 4; $n = 19$). The sorbent device was composed of Amberchrome resin. Animals were treated for 180 min. Blood and plasma samples were obtained at 0, 60, 90, 120 and 180 min for determination of endotoxin, bioactive tumour necrosis factor (TNF) α and white blood cell (WBC) count. Mean arterial pressure (MAP) was monitored continuously and the 7-day mortality was recorded.

Results Mean(s.d.) endotoxin level was 1·1(0·9) ng ml^{-1} in group 2 *versus* 0·6(0·4) ng ml^{-1} in group 4. TNF at 90 min was 12(17) units ml^{-1} in group 2 and 26(39) units ml^{-1} in group 4. WBC count at 60 min was 3·4(1·6), 1·7(0·3), 4·9(0·5) and 2·3(0·8) per μl in groups 1, 2, 3, and 4 respectively ($P < 0{\cdot}05$, group 2 *versus* all). MAP at 60 min was 59(9), 36(10), 58(12) and 51(11) mmHg in groups 1, 2, 3 and 4 respectively ($P < 0{\cdot}05$, group 2 *versus* all). The mortality rate was 30, 75, 16 and 21 per cent in groups 1, 2, 3 and 4 respectively ($P < 0{\cdot}05$, group 2 *versus* all). Regardless of the type of treatment, the mean endotoxin level in surviving animals was lower than that in dying animals (0·5(0·4) *versus* 1·3(1·0) ng ml^{-1}; $P < 0{\cdot}05$).

Conclusion In this model of Gram-negative septic shock, the use of CP + SA significantly reduced the mortality rate. This effect may be mediated by the ability of the sorbent device to absorb endotoxin. This treatment also effectively counteracted the endotoxin infusion-mediated hypotension and leucopenia.

Hyaluronic acid solution decreases the healing of colonic anastomoses in rats with bacterial peritonitis

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Background Hyaluronic acid (HA) reduces postsurgical adhesion formation. A reduction in intra-abdominal adhesion and abscess formation has been demonstrated in a rat peritonitis model using a 0·4 per cent HA solution. Prevention of adhesion formation might have adverse effects on the healing of fresh bowel anastomoses in normal individuals whereas the opposite is suggested for anastomotic healing in an infected environment. The influence of two HA agents on the healing of colonic anastomoses in normal rats and rats with bacterial peritonitis was investigated.

Methods In 72 male Wistar rats the caecum was dissected, ligated and punctured once at the antimesenteric site with a 19-G needle. After operation rats received one intramuscular dose of gentamicin 6 mg kg^{-1}. Twenty-four hours after laparotomy the abdomen was reopened and the caecum was resected. The descending colon was dissected and transected 3 cm proximal to the peritoneal reflection and an end-to-end anastomosis was performed (peritonitis group). In 60 male Wistar rats an end-to-end anastomosis of the colon was performed (control group). Animals in both groups were randomized to receive either a HA/carboxymethyl cellulose film (Seprafilm) (1 × 2 cm wrapped around the anastomosis and 2 × 2 under the midline incision), 8 ml 0·4 per cent HA solution (Sepracoat) or nothing (control subgroup). Half of the animals in each group were killed on day 3 and half on day 7 after operation, and the anastomosis was resected without adhesiolysis. Bursting pressures and breaking strengths were measured. Adhesions and abscesses were scored semiquantitatively.

Results During the experiment 11 rats died in the peritonitis group (15 per cent) and one rat in the control group (2 per cent). There was no significant difference in mortality rate between subgroups. In all subgroups both bursting pressures and breaking strengths were significantly higher on day 7 than day 3 ($P = 0{\cdot}0001$). On day 3 bursting pressures were significantly higher in rats with peritonitis compared with control rats in the HA/CMC subgroup ($P = 0{\cdot}01$) and the control subgroup ($P = 0{\cdot}006$) and not in the subgroup treated with HA solution. On day 7 there was no significant difference in bursting pressure between rats with peritonitis and controls. On both day 3 and day 7 rats with peritonitis treated with HA solution tended to have lower bursting pressures compared with untreated rats with peritonitis (159(17) *versus* 190(11) mmHg and 283(17) *versus* 315(17) mmHg, *P* not significant). There was no significant difference in breaking strengths measured at both time points between groups and subgroups. The lowest rate of intra-abdominal adhesions and abscesses was found in rats treated with the 0·4 per cent HA solution.

Conclusion Early healing of colonic anastomoses is enhanced in rats with bacterial peritonitis. This effect seems to be diminished by intraperitoneal treatment with HA solution.

Effect of carbon dioxide pneumoperitoneum on endotoxaemia, bacteraemia and interleukin 6 levels

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Background Increased intra-abdominal pressure during laparoscopy may lead to bacteraemia and dissemination of infection. This study determined the effect of carbon dioxide pneumoperitoneum on endotoxaemia, bacteraemia and interleukin (IL) 6 levels in an animal model of intra-abdominal infection.
Methods Some 120 Swiss-Albino mice were divided into five experimental groups. Group 1 received a high intraperitoneal bacterial inoculum, consisting of a mean(s.d.) of $1{\cdot}2(0{\cdot}3) \times 10^8$ colony forming units (c.f.u.) per ml followed by laparotomy for 1 and 2 h in subgroups 3A and 3B respectively. Group 2 received a low intraperitoneal bacterial inoculum consisting of $1{\cdot}2(0{\cdot}3) \times 10^4$ c.f.u. ml^{-1} followed by laparotomy for 1 and 2 h in subgroups 2A and 2B respectively. Group 4 received an identical bacterial inoculum followed by carbon dioxide pneumoperitoneum for 1 and 2 h in subgroups 4A and 4B respectively. Group 5 received no bacterial challenge and was subjected to carbon dioxide pneumoperitoneum for 1 and 2 h in subgroups 5A and 5B respectively. Blood samples were taken at 30 and 60 min for measurement of plasma endotoxin levels and blood cultures, and at 60 min for IL-6 determination.
Results Endotoxin levels at 30 and 60 min were significantly higher in subgroup 3B compared with 1B ($P = 0{\cdot}007$, $P = 0{\cdot}02$). The differences in plasma endotoxin level at 30 and 60 min between other subgroups were not significant. There was no difference in serum IL-6 levels between all subgroups. There was a significant difference only in positive blood cultures at 60 min in subgroup 2A *versus* 4A ($P = 0{\cdot}007$). The differences in positive blood cultures between other subgroups were not significant.
Conclusion The results of this study suggest that pneumoperitoneum during severe intra-abdominal infection may aggravate endotoxaemia depending on the severity of infection and the duration of pneumoperitoneum.

Gastric tonometry, cytokines, anaesthesia and complications after colorectal surgery

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Background The value of gastric tonometry, and interleukin (IL) 6 and tumour necrosis factor (TNF) α measurement in prediction of complications after elective colorectal surgery has been estimated.
Methods This was a prospective randomized study of four methods of anaesthesia, involving total intravenous anaesthesia with propofol, epidural and opiate analgesia.
Results Forty-five patients have been recruited so far. A significant advantage has already been accrued in patients having an epidural, being associated with shorter operations (median 126 (range 60–280) *versus* 180 (86–240) min; $P < 0{\cdot}01$), less blood loss (median 710 (range 200–2235) *versus* 1325 (250–2725) ml; $P < 0{\cdot}05$), better pain relief (83 *versus* 37 per cent; $P < 0{\cdot}02$) and a tendency to return home earlier. There was a steady rise in TNF-α levels after operation but IL-6 concentration peaked on the first postoperative day. Only IL-6 levels predicted postoperative complications (complications *versus* no complications: day 1, 200 (range 72–600) *versus* 97 (0–595) pg ml^{-1}, $P < 0{\cdot}05$; day 7, 49 (7–150) *versus* 11 (3–93) pg ml^{-1}, $P < 0{\cdot}002$). No similar association was found with TNF-α. There was a fall in gastric intramucosal pH (pH$_i$) during operations (median fall pH 0·08) but this had no relation to type of anaesthesia, blood loss, length of operation or the development of postoperative complications.
Conclusion Plasma levels of IL-6 can predict surgical complications after elective colorectal surgery. Gastric tonometry was unhelpful, which probably reflects good intraoperative anaesthetic practice.

Differential T helper 1 cell cytokine synthesis of human memory (CD45RO) *versus* naive (CD45RA) T cells following major burn trauma

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Background Based on patterns of expression of CD45 isoforms, T cells can be divided into functionally distinct and largely reciprocal subpopulations. The CD45RA-positive subset identifies primary (naive) T cells, while CD45RO cells are considered to be mostly primed (memory) T cells. It was hypothesized that under stressful conditions an excessive release of CD45RA-positive T cells should occur. It was the objective of this study to obtain further insight into the trauma-induced constitutional changes of proinflammatory cytokine patterns via analysis of CD45RA-positive and CD45RO-positive subsets in CD4-positive *versus* CD8-positive T cells. A newly developed technique of immunofluorescence was used to detect individual cytokine producing cells via flow cytometric analysis with monoclonal antibodies as specific reagents.
Methods Fifteen healthy controls and ten patients following major burn injury (mean(s.d.) age 39(5) years; mean(s.d.) Injury Severity Score 51(4)) had immunological screening on days 1, 5, and 7 after trauma. The *in vitro* capacity of peripheral blood mononuclear cells triggered with ionomycin (1 μmol l^{-1}) and phorbolester (5 ng ml^{-1}) to produce the T helper 1 cell cytokines interferon (IFN) γ and interleukin (IL) 2 was investigated.
Results

		Percentage of cytokine-positive cells			
T cell subset	Cytokine	Day 1	Day 5	Day 7	Control
CD4/45RO	IFN-γ	21·7(2·1)	20·0(1·2)‡	17·9(1·8)‡	26·6(1·5)
CD4/45RA	IFN-γ	2·2(0·3)†	2·4(0·5)*	3·3(0·8)†	1·0(0·2)
CD8/45RO	IFN-γ	41·4(7·3)	38·4(5·5)	41·1(5·2)	39·5(3·5)
CD8/45RA	IFN-γ	16·0(3·7)‡	16·5(3·3)‡	15·8(3·6)†	5·6(0·6)
CD4/45RO	IL-2	33·9(2·8)	35·5(7·4)	33·5(8·4)	38·9(2·2)
CD4/45RA	IL-2	8·3(1·4)†	15·6(6·7)	26·7(7·6)*	14·8(1·4)
CD8/45RO	IL-2	16·3(5·8)	25·3(8·2)*	26·7(7·6)*	9·7(1·6)
CD8/45RA	IL-2	6·8(1·8)*	18·6(10·2)*	10·7(1·8)†	1·4(0·4)

Values are mean(s.d.). *$P < 0{\cdot}05$, †$P < 0{\cdot}01$, ‡$P < 0{\cdot}001$ *versus* control

Conclusion These data demonstrate that helper (CD4 positive) as well as cytotoxic (CD8 positive) (naive) T cells (CD45RA positive) are capable of enhancing their IFN-γ synthesis under traumatic stress compared with those of healthy blood donors, while the IFN-γ response of the memory subtype (CD45RO positive) was diminished (CD4 positive) or remained unchanged (CD8 positive). The predominantly affected cellular source of IL-2 following burn trauma has been shown to be the CD8-positive CD45RA-positive lymphocyte. Further analysis of these data revealed that an augmented percentage of CD45RA-positive IL-2 and IFN-γ producing cells (compared with that in survivors) is predictive for non-survival after trauma. It is concluded that cytoplasmic T cell cytokine analysis represents a valuable screening method to predict biological aberrations and catastrophes.

Immunosuppressive effects of glycine on cytokine production of lipopolysaccharide-stimulated human blood monocytes

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Background Monocytes play a central role in both specific and non-specific immunity against bacterial, viral and fungal infection. The non-essential amino acid glycine (GLY) has been shown to be protective against endotoxic shock in the rat. Since little is known about the influence of GLY on cytokine production by human monocytes, the role of GLY on monocytes from healthy donors was examined *in vitro* and *ex vivo*.

Methods Monocytes were isolated from 500 ml heparinized blood of healthy donors by counterflow centrifugation at a purity of about 85–95 per cent and cultured in RPMI 1640 medium with various concentrations of GLY (0, 0·13 (physiological concentration), 2, 5 and 10 mmol l^{-1}). To prevent cell activation monocytes were preincubated in Teflon dishes for 40 h. Afterwards monocytes were stimulated with lipopolysaccharide (LPS) 1 μg ml^{-1}; supernatants were collected after 1, 6, 12, 24, 48 and 72 h and measured for tumour necrosis factor (TNF) α and interleukin (IL) 10 by enzyme-linked immunosorbent assay. Whole blood assays (blood from healthy donors) were performed using heparinized vacutainer tubes. Blood was preincubated for 6 h with GLY (plasma concentration 1 and 2 mmol l^{-1}) and subsequently treated with LPS 1 μg ml^{-1}. Supernatants were analysed for TNF-α, IL-β and IL-10 after 1, 3, 6 and 12 h of LPS treatment.

Results Stimulation of purified monocytes with LPS led to maximum production of TNF-α after 6 h which was dose dependently reduced by increasing the GLY concentration in the culture medium (2 mmol l^{-1}, −40 per cent; 10 mmol l^{-1}, −89 per cent; $P<0·01$). The effect of IL-10 after LPS stimulation was time dependent. A high GLY load caused an increased IL-10 production (+304 per cent) 6 h after LPS stimulation, but blocked IL-10 production after 24 h (−56 per cent) after LPS stimulation. In a similar manner, whole blood LPS stimulation reduced TNF-α concentration ($P<0·01$) as well as IL-β level ($P<0·05$) with GLY 2 mmol l^{-1} by 3 h. IL-10 production was significantly enhanced 6 h after LPS stimulation ($P<0·05$).

Conclusion These data demonstrate that GLY affects cytokine production of monocytes in the direction of immunosuppression.

Preoperative immunotherapy with interleukin 2 and infective complications in colorectal surgery

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Background The immunological response is essential in controlling postoperative infections and normal repair of surgical wounds. It is necessary to increase the immune response in oncological colorectal surgery in the hope of controlling neoplastic cells and reducing infective complications which are frequent in this kind of surgery. The incidence of infective complications was evaluated in patients undergoing elective colorectal surgery with or without preventive treatment with interleukin (IL) 2. Patients with occlusion, perforation and bleeding, second tumours, past or present steroid therapy and patients older than 80 years were excluded.

Methods In the treated group there were 40 patients, of mean age 60·3 (range 36–80) years. IL-2 immunotherapy was 9 000 000 units twice a day for 3 days in the preoperative period. The control group included 73 consecutive patients, of mean age 65·6 (range 36–80) years, undergoing elective surgery in the same period but without immunological therapy. All patients received the same intestinal preparation and prophylaxis with cefoxitin.

Results There was one postoperative death from stroke in the treated group and no surgical deaths in the control group. There were a number of infective complications after surgery. One of 40 patients in the IL-2 group developed sepsis (pelvic infection) and five (7 per cent) of 73 in the control group (one associated with complete anastomotic wound leakage and three with intraperitoneal sepsis). One of 40 in the IL-2 group developed a wound infection (the patient with sepsis) and 12 (16 per cent) of 73 in the control group ($P=0·0032$). One of 40 patients in the IL-2 group suffered anastomotic leakage of radiological but not clinical significance and two (3 per cent) of 73 in the control group (one associated with sepsis). Other associated infections were four of 40 *versus* seven (10 per cent) of 73 in the lungs and three of 40 *versus* four (5 per cent) of 73 in the urinary tract.

Conclusion IL-2 is a specific T lymphocyte growth factor, although it induces secretion of other cytokines in a cascade sequence which involves all the immune cells and particularly the macrophage. This activation has a positive role in tissue repair and infection control. The only real risk is an overproduction of IL-6 and tumour necrosis factor by the activated macrophage which induces multiorgan failure syndrome. With the IL-2 dosage currently used and in the authors' clinical experience this possibility is theoretical, while a significant reduction in surgical infection occurs.

Imaging experimental intra-abdominal abscesses with technetium-99m-PEG-liposomes and technetium-99m-HYNIC-immunoglobulin G

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Background Rapid and accurate localization of intra-abdominal infection remains a challenging problem for nuclear imaging techniques. Two newly developed technetium-99m-labelled agents, technetium-99m-PEG-liposomes and technetium-99m-HYNIC-immunoglobulin (Ig) G, have shown excellent imaging of experimental focal infection, but have not yet been studied in the detection of abdominal abscesses. Liposomes are particularly attractive, as they offer the opportunity for targeted drug delivery. The performance of these two agents was studied in a rat model of intra-abdominal infection; gallium-67-citrate was included as a reference agent.

Methods On day 0, intra-abdominal infection was induced in rats by caecal ligation and puncture. The following day, the caecum was resected and the abdominal cavity was rinsed with normal saline. On day 8, rats were randomized and injected intravenously with technetium-99m-PEG-liposomes, technetium-99m-HYNIC-IgG or gallium-67-citrate ($n=12$ in each group). Rats were imaged at regular intervals for 24 h. After the final image at 24 h after injection, rats were killed and the uptake of the radiolabel in dissected tissues was determined. Macroscopic abnormalities and focal uptake on the images were scored semi-quantitatively.

Results Some 85 per cent of rats showed intra-abdominal abscess formation. Abscesses were clearly delineated by the three agents from 4 h after injection. Liposomes, IgG and gallium-67 all showed high absolute uptake in the abscess (mean(s.d.) 2·3(0·3), 2·8(0·3) and 2·8(0·4) per cent ID g^{-1} respectively), and did not differ significantly. Focal uptake of all three radiopharmaceuticals correlated well with the severity of inflammation (for liposomes $r=0·65$, $P<0·03$; for IgG $r=0·61$, $P<0·05$; for gallium-67 $r=0·73$, $P<0·02$).

Conclusion Technetium-99m-labelled PEG-liposomes and technetium-99m-HYNIC-IgG show high focal uptake in experimental intra-abdominal abscess, similar to the standard agent gallium-67. The uptake correlated well with macroscopic inflammation. The lower radiation exposure and more favourable physical properties of technetium-99m make labelled liposomes and IgG attractive agents for imaging abdominal infection. In addition, PEG-liposomes could be valuable in the treatment of abdominal inflammation by enhanced local delivery of incorporated drugs.

Correlation between antithrombin III levels and outcome and severity of diffuse peritonitis

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Background Coagulopathy is a frequent complication in diffuse peritonitis. Endotoxin initiates the coagulation cascade. Subse-

quently, the consumption of anticoagulative factors leads to severe coagulopathy and plays a major role in septic organ failure.
Methods The correlation between antithrombin III (AT-III) levels and the severity and outcome of diffuse peritonitis was studied retrospectively in 88 patients. The severity of peritonitis was determined by the Mannheim Peritonitis Index (MPI), the Acute Physiology And Chronic Health Evaluation (APACHE) II score and the Sepsis Severity Score (SSS).
Results At the onset of the intra-abdominal infection, a severe decrease in AT-III level was noted to a mean of 62 per cent in survivors and 57 per cent in non-survivors. On day 1, the AT-III levels in patients with scores of less than 20, 20–30 and greater than 30 were 69, 61 and 57 per cent (MPI), 62, 60 and 55 per cent (APACHE II day 1), and 74, 56 and 56 per cent (SSS day 1) respectively. The lowest AT-III levels were 52 per cent in survivors and 45 per cent in non-survivors ($P<0\cdot05$), and for the above-mentioned severity groups 55, 49 and 47 per cent (MPI), 53, 48 and 42 per cent (APACHE II day 1), and 61, 49 and 44 per cent (SSS day 1) respectively. The differences between the SSS and APACHE II groups with scores of less than 20 and greater than 30 were significant ($P<0\cdot05$). The respective AT-III values were measured before substitution.
Conclusion These results indicate that there are correlations between AT-III levels, and outcome and severity of peritonitis.

Shoemaker criteria as a prognostic marker for postoperative morbidity and mortality

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Background The Shoemaker high-risk criteria have been proposed to predict postoperative morbidity and mortality in surgical patients. This study was designed to evaluate prospectively the usefulness of these criteria as a prognostic marker.
Methods In a prospective study, patients undergoing abdominal, non-vascular surgery were screened before operation for the number of Shoemaker criteria present (from a list of 13 criteria). At 24 h an Acute Physiology And Chronic Health Evaluation (APACHE) II and multiple organ failure (MOF) score were calculated and correlated with the Shoemaker criteria, using the Pearson correlation coefficient. The survival at day 28 was related to the number of Shoemaker criteria present using log rank analysis, Cox multiple regression analysis, and receiver–operator characteristic (ROC) curves.
Results Some 433 patients were assessed, of whom 412 were evaluable. The majority (52 per cent) had only one criterion. An increasing Shoemaker score was related to an increased mortality rate, calculated by log rank analysis. The presence of shock and respiratory failure were the most important criteria calculated by regression analysis. The mean(s.d.) area under the ROC curve was 0·72(0·04) for predicting death. The correlation coefficients of the Shoemaker score related to the APACHE II score and the MOF score were 0·308 ($P<0\cdot001$) and 0·305 ($P<0\cdot001$) respectively.
Conclusion The Shoemaker criteria can be used as a quick preoperative prognostic marker for identification of high-risk surgical patients. However, no clear relation exists with the severity scores during the first 24 h after operation.

Treatment of *Candida* peritonitis

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Background *Candida* peritonitis is a severe disease with a high associated mortality rate. The management of these critically ill patients is still a matter of debate.
Methods Since 1980 all patients with diffuse peritonitis were treated by daily relaparotomy and abdominal lavage. During surgical intervention, aspirates of fluid and samples of peritoneum were obtained. The clinically suspected diagnosis of invasive mycosis was verified by histological examination. Patients received either fluconazole (initially 800 mg followed by 400 mg daily) or amphotericin B and flucytosine (0·5–1 mg per kg body-weight). At the time of infection of the first four patients effective antimycotics were not available. The course of infection was followed from peritoneal samples taken during relaparotomy.
Results Some 265 patients with diffuse peritonitis were treated. The infection was caused by *Candida* spp. in 19 cases (7·1 per cent). The mean(s.d.) age of these patients was 59·4(24·8) years; there were 11 men and eight women. Seventy-nine abdominal lavages were performed. The isolates were *C. albicans* ($n=13$), *C. tropicalis* ($n=3$), *C. glabrata* ($n=2$) and *C. pulcherrima* ($n=1$). Antifungal treatment included application of fluconazole ($n=9$) or amphotericin B and flucytosine ($n=6$). Resolution of infection occurred in 15 cases. Four patients did not receive antimycotics. Eight patients survived.
Conclusion A deep invasive mycosis of the abdominal cavity can be resolved by aggressive surgical intervention in combination with antimycotic substances. Treatment with fluconazole is as effective as application of amphotericin B and flucytosine. The substantially reduced general condition of the patients leads to high mortality rates despite resolution of infection.

Surgical treatment of acute purulent mediastinitis

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Background Purulent mediastinitis can occur as a complication of oropharyngeal and cervical infections or after open heart surgery. Delayed diagnosis and inadequate drainage are the main causes of a high published mortality rate (up to 50 per cent).
Methods The primary management of purulent mediastinitis in this institution includes partial or complete sternotomy, withdrawal of all foreign bodies, radical debridement of the mediastinum and, if necessary, revision of the pericardium and pleural space. A massive dose of broad-spectrum antibiotics is given and modified according to the microbiological results. The second step of treatment is an open programmed irrigation with daily revision and debridement. Intensive care monitoring and ventilation are needed.
Results During a period from 1986 to 1996 11 patients (nine men; aged from 24 to 71 years) with purulent mediastinitis were treated. Aetiology was a descending necrotizing mediastinitis because of oropharyngeal infection in five cases and there were six postoperative infections after open heart surgery (coronary artery bypass graft, aortic valve replacement). Microbiological features included *Streptococcus* spp., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Candida albicans*, *Enterobacter* spp. and nocardiosis. Intensive care unit stay was from 2 days up to 6 months. Four of the 11 patients died. One patient died from myocardial infarction with low cardiac output syndrome and three patients developed multiorgan failure due to generalized sepsis.
Conclusion Active surgical intervention can improve the clinical outcome of patients with purulent mediastinitis. Unfortunately, a high mortality rate remains and mediastinitis is still a life-threatening condition.

Computed tomography: a vital adjunct in the management of complex postoperative abdominal sepsis

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Background Clinical diagnosis of complex postoperative abdominal sepsis is made difficult by previous surgery and by complications such as organ failure, line sepsis, fistulas or malnutrition, but it is established that recovery is unlikely if abdominal sepsis continues. This unit provides a national tertiary referral

service for these patients. A 2-year prospective evaluation of the use of routine admission abdominal computed tomography (CT) to detect previously unidentified abdominal sepsis is reported.
Methods Early abdominal CT with gastrointestinal contrast enhancement was performed in 32 instances in 28 patients admitted to the unit with suspected abdominal sepsis from October 1995. Median patient age was 49 (range 22–75) years and 26 fulfilled Bone's criteria for sepsis. CT identified abdominal collections in 21 of 32 instances but failed in five of 32; in the latter cases collections were detected at laparotomy performed for failure of conservative treatment. After six of 32 scans patients were treated conservatively with success.
Results Immediate radiological drainage was performed with clinical benefit in 11 of 21 cases and surgical treatment was necessary only in a further five of 21 patients in whom radiological drainage was not appropriate (multiple or inaccessible collections). In five of 21 cases, small superficial collections connected to draining fistulas were managed conservatively. CT revealed radiologically drainable abdominal collections on three of 31 occasions in patients who did not satisfy the Bone criteria for sepsis.
Conclusion Abdominal CR detects previously unrecognized collections in two-thirds of patients transferred for further management of the complications of abdominal surgery; radiological drainage is sufficient in a majority of these. A low threshold for CT and drainage should be maintained in patients following complicated abdominal surgery.

In vitro improvement of transendothelial migration of polymorphonuclear neutrophils in patients with cirrhosis by granulocyte colony stimulating factor

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Background Patients with cirrhosis present with a high incidence of bacterial infections. They have a deficient cell influx towards infective sites. This study assessed neutrophil adhesion and transendothelial migration *in vitro* and evaluated the possible immunostimulatory effect of granulocyte colony stimulating factor (G-CSF).
Methods Polymorphonuclear neutrophil (PMN) adhesion and transendothelial migration was studied in patients with cirrhosis ($n = 14$) and healthy controls ($n = 14$) using the microvascular endothelial cell line HMEC-1. PMNs were isolated from whole blood by density gradient centrifugation and labelled with the fluorescent dye BCECF-AM. For adhesion assays, 10^5 PMNs per well were co-incubated for 1 h with resting or tumour necrosis factor (TNF) α-stimulated HMEC-1 cells. Unattached cells were removed and the number of adherent PMNs per well was calculated with a microtitre plate fluorimeter. For migration experiments, 2×10^5 PMNs were added into a Transwell system over TNF-α-stimulated endothelium and allowed to migrate for 2 h in response to FMLP in the lower chamber. Then, transmigrated PMNs were harvested and counted. G-CSF 100 ng ml^{-1} was added to neutrophils at the start of the assay and was present throughout.
Results Mean(s.d.) neutrophil adhesion was increased in patients with cirrhosis compared with controls to both resting (18·9(7·2) $\times 10^3$ *versus* 10·8(3·0) $\times 10^3$ PMNs per well; $P < 0·01$) and TNF-α-stimulated (27·7(7·1) $\times 10^3$ *versus* 18·6(6·1) $\times 10^3$ PMNs per well; $P < 0·01$) HMEC-1 cells. G-CSF significantly increased PMN adhesion in controls but not in patients with cirrhosis. Neutrophil transendothelial migration was decreased in patients with cirrhosis (36·5(15·5) $\times 10^3$ PMNs per well) compared with controls (60·2(23·3) $\times 10^3$ PMNs per well) ($P < 0·01$). G-CSF significantly enhanced neutrophil transmigration both in patients with cirrhosis (44·4(17·7) $\times 10^3$ PMNs per well) and in healthy controls (71·5(27·3) $\times 10^3$ PMNs per well) ($P < 0·01$).
Conclusion G-CSF enhances neutrophil transendothelial migration in patients with cirrhosis despite having no effect on neutrophil adhesion. This suggests that G-CSF is able to increase neutrophil recruitment into local infective sites in these patients.

Type II diabetes intensifies the response to intestinal ischaemia–reperfusion

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Background It has been shown that granulocytes isolated from diabetic patients display a greater degree of activation than those from non-diabetics. In addition, both type I and type II diabetes are associated with increased lipid peroxidation and higher levels of circulating adhesion molecules. Neonatal streptozotocin (STZ) administration in rats leads to mild insulin deficiency in adults with normal blood glucose levels, and is accepted as a model of type II diabetes. In this study possible differences in the systemic release of some inflammatory mediators after intestinal ischaemia–reperfusion (I–R) between control and type II diabetic rats were investigated.
Methods STZ 0 or 30 mg kg^{-1} was injected into Wistar rats on the day of birth. Two-month-old animals, both control and type II diabetic (normoglycaemic), were randomly separated into two groups. Group 1 rats underwent a 60-min period of gut ischaemia by clamping the superior mesenteric artery. Five minutes after reperfusion, rats were killed and plasma samples were obtained from portal vein (PV), and infrahepatic (IHC) and suprahepatic (SHC) cava. Group 2 rats underwent sham operation. Nitric oxide was measured as NO_2^- and NO_3^- by the Griess reaction. Lipid hydroperoxides (LPO) were determined spectrophotometrically using a commercially available kit. Tumour necrosis factor (TNF) α, 75-kDa receptor (TNF-R2), 60-kDa receptor (TNF-R1) and intercellular adhesion molecule (ICAM) 1 were measured by enzyme-linked immunosorbent assay.
Results After I–R, diabetic rats showed increased plasma concentrations of LPO, nitric oxide, ICAM-1 (mean(s.d.) 0·514(0·083) *versus* 0·046(0·011) ng ml^{-1} (IHC); 0·574(0·075) *versus* 0·037(0·009) ng ml^{-1} (SHC); and 0·528(0·067) *versus* 0·033(0·009) ng ml^{-1} (PV); $n = 10$, all $P < 0·01$), TNF-α (42·4(5·7) pg ml^{-1} (IHC), 248·4(28·2) pg ml^{-1} (SHC) and 33·6(4·0) pg ml^{-1} (PV) in diabetic rats *versus* undetectable in control rats; $n = 10$), TNF-R1 (0·179(0·024) *versus* 0·023(0·011) ng ml^{-1} (IHC); 0·233(0·032) *versus* 0·033(0·005) ng ml^{-1} (SHC); 0·206(0·034) *versus* 0·039(0·023) ng ml^{-1} (PV); $n = 10$, all $P < 0·05$) whereas TNF-R2 did not differ between groups. Both TNF-α and nitric oxide plasma levels were higher in SHC than in IHC and PV after I–R, pointing to the liver as an important source for both mediators.
Conclusion Pre-existing type II diabetes intensifies the inflammatory response after intestinal I–R.

Kinetics of tumour necrosis factor α, interleukins 1β, 6, 8 and 10, phospholipase A_2 and neopterin in surgical treatment of diffuse peritonitis: results of bedside monitoring

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Background This study evaluated cytokine and mediator kinetics during primary and scheduled surgical interventions in treatment of patients with diffuse peritonitis to establish bedside monitoring.
Methods Eleven patients with necrotizing pancreatitis (median Ranson score 7 (range 6–8)) and one patient with postoperative peritonitis underwent 19 operations combined with preoperative intraoperative and postoperative sequential blood sampling. Serum concentrations of tumour necrosis factor (TNF) α, interleukins (ILs) 1β, 6, 8 and 10, neopterin and phospholipase A_2 (PLA_2) were measured.

Results Detectable ETX concentrations were less than 4 units ml^{-1} in all measurements; the highest values were found before operation. TNF-α concentration increased at operation to a median (interquartile range) of 58·5 (28·2–92·8) pg ml^{-1} with a similar postoperative course (53·8 (10·0–104·0) pg ml^{-1}. IL-1β level rose at operation to 15·6 (3·6–17·8) pg ml^{-1} ($P<0{\cdot}05$). IL-6 was increased in all postoperative samples, and was maximal after 3·5 h (1327 (550–2020) pg ml^{-1}; $P<0{\cdot}05$). High levels of IL-8 were seen at operation after 1·5 h (72 (43–142) pg ml^{-1}; $P<0{\cdot}05$) and 2 h (121 (55–157) pg ml^{-1}; $P<0{\cdot}05$) and IL-8 expression increased again after operation to a maximum (183 (72–299) pg ml^{-1}; $P<0{\cdot}05$) after 3·5 h. IL-10 showed a preoperative peak level (49·7 (6·9–168·0) pg ml^{-1}) and at operation was 22·6 (11·8–89·8) pg ml^{-1} ($P<0{\cdot}05$). PLA$_2$ was pathologically high continuously, but not significantly so. Neopterin showed highest concentrations (72·0 (35·0–86·2) nmol l^{-1}; $P<0{\cdot}05$) during operation. Rescheduled operation appeared to have no influence on long-term cytokine course. Some 12 h before operation IL-6 correlated with Acute Physiology And Chronic Health Evaluation (APACHE) II score ($r=0{\cdot}55$, $P<0{\cdot}05$). Significant correlations were found between TNF-α concentration and IL-6 expression ($r=0{\cdot}67$, $P<0{\cdot}01$). IL-6 level correlated significantly with IL-8 expression ($r=0{\cdot}67$, $P<0{\cdot}01$). There were correlations between IL-10 expression and IL-6 concentration ($r=0{\cdot}95$, $P<0{\cdot}001$) and IL-8 values ($r=0{\cdot}63$, $P<0{\cdot}02$). Early intraoperative (first 15 min) IL-10 level correlated with IL-6 expression ($r=0{\cdot}96$, $P<0{\cdot}001$). After 30 min, IL-8 level correlated with IL-6 expression ($r=0{\cdot}61$, $P<0{\cdot}05$) and IL-20 values ($r=0{\cdot}64$, $P<0{\cdot}05$). The correlation between IL-6 concentration and IL-10 expression persisted into the early postoperative period (3 min) ($r=0{\cdot}94$, $P<0{\cdot}001$). In the third hour after operation TNF-α values correlated with the time span of operation ($r=0{\cdot}63$, $P<0{\cdot}05$). There was a prolonged correlation between IL-8 concentration and IL-10 expression ($r=0{\cdot}60$, $P<0{\cdot}03$).

Conclusion In the surgical treatment of critical care patients, established scoring systems like APACHE II can be supplemented with the response of the proinflammatory and anti-inflammatory activities of cytokines. Bedside monitoring based on cytokines could be established in daily clinical routine. However, because of the financial and personal costs, interdisciplinary and multicentre cooperation is necessary.

Experimental study of the effect of nitric oxide inhibition on mesenteric blood flow and interleukin 10 levels in endotoxin challenge

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Background The effects of two nitric oxide synthase (NOS) inhibitors, L-NAME and aminoguanidine (AG), on mesenteric blood flow (MBF) and interleukin (IL) 10 levels in lipopolysaccharide (LPS) challenge were evaluated.

Methods Swiss albino mice were divided into two groups (pretreatment and post-treatment). In the pretreatment group, at 0 h animals were injected with AG 20 mg kg^{-1}, L-NAME 20 mg kg^{-1} or saline. At 20 min saline was injected into half of the animals and LPS 10 mg kg^{-1} was injected into the other half. At 140 min a perivascular Doppler ultrasonic probe was placed around the superior mesenteric artery to measure MBF. Following this, blood samples were drawn for measurement of IL-10 levels. In the post-treatment group, at 0 h LPS 10 mg kg^{-1} or saline was injected. At 20 min, AG 20 mg kg^{-1}, L-NAME 20 mg kg^{-1} or saline was injected. At 120 min, the procedures described above were repeated.

Results In both pretreatment and post-treatment groups LPS significantly decreased MBF in the saline group ($P<0{\cdot}001$ and $P<0{\cdot}0002$ respectively). Both NOS inhibitors were effective in preventing this decrease, administered as either pretreatment or post-treatment when compared with corresponding saline groups ($P<0{\cdot}05$ for any combination). Post-treatment with either NOS inhibitor did not prevent the decrease when compared with the saline–saline group ($P=0{\cdot}0069$ *versus* LPS–AG and $P=0{\cdot}0015$ *versus* LPS–L-NAME) whereas pretreatment was also effective ($P<0{\cdot}05$ for both). In both pretreatment and post-treatment groups LPS significantly increased IL-10 levels compared with those in the corresponding saline groups ($P<0{\cdot}05$ for any combination). In the pretreatment groups, comparison of LPS groups showed that the mean IL-10 level in the saline–LPS group was significantly lower than that in the L-NAME–LPS group ($P=0{\cdot}011$). In the post-treatment animals there was no significant difference between the three LPS groups.

Conclusion NOS inhibition before LPS challenge prevents the subsequent decrease in MBF and increases IL-10 levels, but inhibition after LPS challenge is not effective. L-NAME is more powerful in increasing IL-10 levels than AG.

Adrenaline tolerance and endotoxin tolerance differentially modulate serum cytokine levels to lipopolysaccharide challenge in a murine model

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Background Cytokines are the primary mediators of sepsis syndrome. Adrenaline tolerance increases survival in endotoxic shock models. In this study, the effect of adrenaline and endotoxin tolerance on major cytokine levels in lipopolysaccharide (LPS) challenge was determined.

Methods Adrenaline tolerance was developed by injecting adrenaline 0·01 mg kg^{-1} to Swiss albino mice, gradually increasing the dose to 2 mg kg^{-1} over 5 days. Endotoxin tolerance was developed by injecting saline for 4 days and LPS 1 mg kg^{-1} on the fifth day. Control animals were injected with saline for 5 days. Some 72 h after completion of injections, saline was injected into half of the animals in each group and LPS 20 mg kg^{-1} into the other half. Peak serum levels of tumour necrosis factor (TNF) α, (IL) 1β, IL-6, IL-10 and IL-12 were assayed and compared.

Results LPS injection significantly raised the levels of all the cytokines studied in the control and adrenaline-tolerant animals ($P<0{\cdot}05$ for any cytokine). TNF-α, IL-6 and IL-10 levels were significantly lower in endotoxin-tolerant animals than in saline controls after LPS challenge ($P<0{\cdot}05$ for any cytokine). Interestingly, adrenaline-tolerant animals had significantly higher levels of TNF-α, IL-6 and IL-12 than saline controls in response to LPS challenge ($P<0{\cdot}05$ for any cytokine). Neither adrenaline tolerance nor endotoxin tolerance induced a significant change in IL-1β levels in response to LPS ($P>0{\cdot}05$ for any combination).

Conclusion Adrenaline tolerance primes for an exaggerated release of TNF-α, IL-6 and IL-12 in response to LPS challenge, demonstrating the anti-inflammatory and immunosuppressive roles of adrenaline. Anti-inflammatory effects are not mediated through increased IL-10 release. Endotoxin tolerance selectively modulates cytokine release. The results also suggest that IL-1β might have different regulatory mechanisms than the other cytokines studied.

Effects of extracorporal endotoxin removal on liver haemodynamics in a porcine sepsis model

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Background Endotoxin-induced activation of macrophages followed by release of cytokines and inflammatory mediators has profound effects on liver blood flow and microvascular permeability. Disturbance of liver blood circulation is one of the major events aggravating the early phase of sepsis. This study investigated the effects of extracorporeal bacterial endotoxin absorption (microsphere-based detoxification system, MDS) on liver blood circulation in a porcine sepsis model.

Methods In 14 Landrace pigs (mean body-weight 24 kg), bacterial endotoxin (*Escherichia coli* lipopolysaccharide (LPS) $20\,\mu g\,kg^{-1}\,h^{-1}$) was infused intravenously over 3 h. Liver haemodynamics were determined by measurement of portal venous blood flow, hepatic and portal vascular pressures and liver surface microcirculation (laser Doppler flowmetry). Liver portal vascular resistance was calculated. LPS levels in hepatic venous and arterial blood were determined using *Limulus* amoebocyte lysate. In animals in the therapy group ($n = 8$), an extracorporal endotoxin absorption system based on macroporous cellulose beads with immobilized polyethylenimine (MDS) was used to remove LPS from the circulation.
Results LPS infusion resulted in an initial increase in portal vascular resistance of 26·1 per cent with a simultaneous drop in portal venous blood flow and liver surface microcirculation to 85·5 and 62·2 per cent of baseline respectively ($P < 0{\cdot}05$). Over time, a recovery of portal venous blood flow and hepatic microcirculation was found above baseline until the end of the experiment. The initial drop and the following increase in portal venous blood flow and liver microcirculation were more pronounced in the control group compared with the MDS group. Endotoxin plasma values from arterial and venous blood samples varied widely during LPS infusion in the control and MDS group with marked reduction in the latter.
Conclusion Bacterial endotoxaemia led to a profound disturbance of liver haemodynamics, characterized by a biphasic alteration in liver vascular resistance and surface microcirculation. Extracorporal endotoxin elimination by MDS attenuated endotoxin-induced changes in local liver microcirculation possibly by reducing the LPS-mediated inflammatory response.

Abstracts of posters

Supplemental perioperative oxygen administration increases subcutaneous oxygen tension

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Background Surgical wound infections are common and serious perioperative complications. The major defence against surgical pathogens is oxidative killing by neutrophils. Consequently, the incidence of infection correlates with subcutaneous tissue oxygen tension. The extent to which increasing inspired oxygen tension augments tissue oxygen tension in clinical practice remains unclear. Accordingly, the hypothesis that administration of supplemental perioperative oxygen increases subcutaneous oxygen tension was tested in surgical patients.
Methods Forty patients undergoing colonic resection were studied. They were randomly assigned to 30 per cent ($n = 24$) or 80 per cent ($n = 16$) inspired oxygen (balance nitrogen). Oxygen administration at the designated concentration was continued for 2 h after operation with an AirCare sealed mask system (Apotheus Laboratories, Lubbock, Texas, USA). Arterial partial pressure of oxygen was determined after 1 h of anaesthesia and after 2 h of postoperative recovery. Subcutaneous oxygen tension was recorded from a polarographic electrode (Licox Medical Systems, New York, USA) positioned within a silicone tonometer on the upper arm.
Results Intraoperative arterial oxygen tension was significantly greater in patients given 80 per cent than 30 per cent oxygen (mean(s.d.) 372(107) *versus* 147(40) mmHg). Postoperative arterial oxygen tension was also significantly greater: 188(122) *versus* 112(34) mmHg respectively. Mean intraoperative and postoperative tissue oxygen tensions were also significantly greater during administration of 80 per cent than 30 per cent oxygen (intraoperative 124(46) *versus* 60(28) mmHg; postoperative 72(25) *versus* 53(30) mmHg).
Conclusion These data indicate that supplemental oxygen administration increases tissue oxygen tension from levels associated with frequent infections to levels at which infections are rare.

Intraoperative prophylaxis in patients at risk: a prospective study in colonic surgery

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Background Antimicrobial prophylaxis is particularly effective in colonic surgery. Wound infection rates of about 10 per cent after elective colonic resection are expected. The administration of antibiotics at induction of anaesthesia is most commonly used. In clinical practice there is evidence that the time interval between the first dose, the time of contamination and subsequent infection is uncertain.
Methods A study was therefore conducted in 100 patients undergoing colorectal surgery by giving the first dose of antibiotics during the operation. The study included all types of colonic surgery (for obstruction, diverticulitis and abscesses). Bowel preparation did not include antibiotics. The mean age was 70 years; 95 per cent had an American Society of Anesthesiologists score above 3. The first dose of mezlocillin 4 mg and metronidazole 500 mg was administered 32 (range 5–120) min after the abdominal incision. The operations lasted 146 (range 40–265) min. The second and last dose was given 6–8 h later. Early postoperative feeding was started the day after operation.
Results There were two patients with a postoperative fever above 38°C, six wound infections of the abdominal incision, one anastomotic leakage and no deaths. The mean postoperative stay was 18 (range 7–54) days.
Conclusion In surgical practice there is considerable variation in the timing of the prophylactic administration of antibiotics. The authors therefore propose intraoperative administration as the safest method to reduce bacterial postoperative complications in patients at risk.

Human β-defensin expression in burned and uninjured skin

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Background Defensins are a family of cationic antimicrobial peptides which are part of a non-specific chemical defence system secreted by non-lymphoid cells. Two human β-defensins have been identified. Human β-defensin 1 (hβD-1) has been detected in urogenital, gastrointestinal and pulmonary epithelia, but not in skin. Human β-defensin 2 (hβD-2) is produced by keratinocytes and is the only antimicrobial peptide that has been identified in human skin. Both β-defensins have potent bactericidal activity against a wide spectrum of Gram-positive, Gram-negative and fungal organisms, including *Escherichia coli*, *Pseudomonas*, *Staphylococcus* and *Candida*. The combination of the loss of skin barrier, and failure of both local and systemic immunity, predisposes the burn patient to an increased risk of infection.
Methods Expression of hβD-1 and hβD-2 in the wound of eight patients with full-thickness burns was examined. At the time of wound excision, samples were obtained from each patient for measurement of hβD-1 and hβD-2 expression from both the burn wound and from normal skin. Total RNA was isolated, purified and then subjected to reverse transcriptase–polymerase chain reaction for hβD-1, hβD-2 and three control genes.
Results Single bands representing hβD-1 and hβD-2 expression were found in normal skin; however, only hβD-1 was identified in full-thickness burn wounds. Expression of the control genes was found in both the burn wounds and in normal skin.
Conclusion It is proposed that β-defensins play a protective role in preventing infection within burn wounds and that altered expression of these peptides could promote local overgrowth of micro-organisms. The broad antimicrobial properties of defensins, their chemical resistance and their lack of antigenicity

suggest that they may also be useful as antimicrobial agents for prophylaxis and treatment of burn wound infections.

Surgical intervention in patients with methicillin-resistant *Staphylococcus aureus*

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Background The worldwide spread of methicillin-resistant *Staphylococcus aureus* (MRSA) had led to important therapeutic problems. The optimal timing for surgical treatment in these patients is still uncertain.
Methods All patients with microbiological evidence of MRSA were followed consecutively in this department. The analysis of data included history, previous and concomitant medication, and microbiological and clinical course. After isolation of MRSA, all patients with signs of infection were treated for 5–10 days with antibiotics shown to be sensitive by antibiogram accompanied by daily anti-infective washing of the skin. During infection, surgical procedures were performed under antibiotic medication. After antibiotic treatment follow-up was done by taking swabs of different body areas every 3 days. The infection was resolved when MRSA was not isolated any more in three following swab collections.
Results Between 1 January 1994 and 30 September 1997, 60 cases of MRSA infection occurred. The mean(s.d.) age of the patients was 64·1(11·9) years; there were 34 men and 26 women. MRSA was frequently isolated in tracheal aspirate ($n = 44$), skin ($n = 26$), wound area ($n = 21$), blood culture ($n = 9$) and drains ($n = 4$). Twenty-five patients underwent surgical procedures during or shortly after the infection with MRSA: amputation ($n = 14$), mesh graft transplantation ($n = 5$), laparotomy ($n = 4$) and thoracotomy ($n = 2$). In ten cases the infection spread into the surgically treated area; six of these patients died and in four patients the infection resolved.
Conclusion Surgical intervention in patients with MRSA is associated with a high rate of infection of the surgically treated areas. Elective surgery in these patients should be avoided.

Synchronous appearance of high interleukin 6 plasma concentrations and low responsiveness of peripheral blood cells to lipopolysaccharide following surgical trauma

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Background The mechanisms of postoperative immunosuppression are not completely understood. Changes in cytokine production (interleukin (IL) 6, tumour necrosis factor (TNF) α, IL-10) were investigated in whole blood of patients who had major abdominal operations and the results were related to the immediate immune response to surgical trauma determined by measuring plasma IL-6 concentrations.
Methods Heparinized blood was drawn from 40 patients before the operation, 6 h after skin incision and on the third day after operation. From five patients blood samples were also collected at 1, 2, 3, 4 and 5 h after skin incision. Lipopolysaccharide (LPS) 10 ng ml^{-1} was added and samples were incubated at 37°C and 5 per cent carbon dioxide. Cytokine concentrations in the plasma were assayed (TNF-α and IL-6 after 5 h, IL-10 after 24 h of incubation) by enzyme-linked immunosorbent assay (IL-6 and TNF-α at all time points, IL-10 before operation and on day 3). Serum IL-6 was measured by the Immulite technique. IL-6 messenger RNA (mRNA) was assessed by reverse transcriptase–polymerase chain reaction in peripheral blood mononuclear cells 5 h after skin incision.
Results Production of TNF-α and IL-6 after stimulation with LPS decreased significantly in whole blood drawn 6 h after skin incision and increased on postoperative day 3. The mean(s.d.) consecutive values were 10 686(9403), 3601(4560) and 7029(12 049) pg ml^{-1} for TNF-α, and 78 798(41 451), 21 710(20 299) and 32 247(31 232) pg ml^{-1} for IL-6. IL-10 decreased from 8914(12 242) pg ml^{-1} before operation to 4557(4185) pg ml^{-1} at day 3. A decrease in TNF-α and IL-6 production was already seen at 2 h following skin incision. Serum IL-6 concentrations were increased at 6 h following skin incision from 14(36) to 1071(1570) pg ml^{-1}, peaked at 12 h at 1522(2266) pg ml^{-1} and decreased subsequently to 99(108) pg ml^{-1} at day 3. At 5 h, no IL-6 mRNA was found in circulating blood cells.
Conclusion The capacity of the whole blood to produce cytokines (IL-6, TNF-α, IL-10) was reduced immediately after surgical trauma. In parallel an immediate immune response was found as indicated by high plasma IL-6 concentrations. Circulating IL-6 was not produced by blood cells in response to surgical trauma.

Automated entry of surgical site infection surveillance data: use of an optical scanning system

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Background A project was instituted to monitor continuously the incidence of surgical site infection (SSI) in the Surgical Directorate of The Royal Hospitals, Belfast, UK.
Methods Employing optical scanning technology (Formic for Windows version 2.0; Formic, London, UK) a SSI questionnaire was designed which included relevant data modelled on the National Nosocomial Infections Surveillance System for Surgical Site Infections, including the SSI risk index (Hospital Infections Program; Centers for Disease Control, Atlanta, Georgia, USA). Staff of the surgical directorate were responsible for completion of the questionnaires. Infection control staff with the assistance of 'link' nurses coordinated the surveillance. Scanning of completed questionnaires was followed by data processing for validation and correction of errors. Accuracy rates of 99·98 per cent were achieved with this system. The contents of the database were then exported to SPSS software (SPSS, Chicago, Illinois, USA) for analysis.
Results A total of 7666 surgical procedures was recorded (January 1995 to December 1997). The crude SSI rate for all procedures was 2·8 per cent. The SSI rate for clean, clean-contaminated, contaminated and dirty surgery was 1·2, 4·2, 7·0 and 15·0 per cent respectively. Some 26·6 per cent of patients were shaved before operation. SSI rates for shaved and non-shaved patients were 1·9 and 2·0 per cent respectively. Consultant surgeons had lower crude SSI rates (2·6 per cent) compared with senior registrars (4·5 per cent). When the SSI rates were refined using the SSI risk index, the rates were 1·0 per cent, 1·4 per cent (index 0); 4·4 per cent, 6·9 per cent (index 1); and 8·6 per cent, 21·1 per cent (index 2) for consultants and senior registrars respectively. The same trend was observed whether the surgery was elective or emergency.
Conclusion The use of optical scanning technology to process completed surveillance questionnaires automatically has allowed continuous monitoring of SSI in this hospital. This methodology is recommended to those involved with surveillance of nosocomial infections as a method of removing the bottleneck of manual data entry. In addition to general surgery, this system is being employed in cardiac surgery and neurosurgery.

Staphylococcus aureus infection in serious burns: review of 2700 admissions

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Background In recent years at most burn centres, the combination of improved methods of patient care and the practice of isolation of seriously burned patients has resulted in a decreased incidence of infection and in particular of wound infection. Associated with this observation has been a change in pathogens from previously common *Pseudomonas aeruginosa* and other Gram-negative organisms to increases in Gram-positive offenders. The incidence of *Staphylococcus aureus* colonization and infections has been reviewed in consecutive patients admitted to a single burn centre between 1986 and 1997.

Methods Patients were cared for in single-bed isolation rooms during the intensive care phase of treatment. Patients were assigned to specific nursing care teams during each working day and cross-team care was prohibited. Microbial surveillance, consisting of wound surface, sputum amd urine cultures three times weekly, was carried out on patients from admission to discharge. Colonization was defined as isolation from noninfected site and infection was defined using site-specific criteria. Predominant organisms in each culture were subjected to antibiotic sensitivity testing. Oxacillin resistance was used to define *S. aureus* strains resistant to β-lactam antibiotics (methicillin-resistant *S. aureus*, MRSA). Demonstration of MRSA colonization or infection did not alter isolation practices.

Results *S. aureus* colonization was observed in 1220 admissions (45 per cent). *S. aureus* caused 391 infections in 275 patients (10 per cent). The respiratory tract was the most common site (63 per cent). *S. aureus* infections represented 31 per cent of all infections during the period. *S. aureus* was the most common pathogen identified and was more than twice as frequent as the next cause of infection. MRSA colonization was identified in 360 patients (13 per cent). Most MRSA infections occurred in 112 patients (4 per cent). The mortality rate in *S. aureus*-infected patients was not greater than that predicted on the basis of severity of injury and age. MRSA infection did not change this finding.

Conclusion These results identify *S. aureus* as the principal pathogen in this cohort. MRSA colonization or infection was not found to cause outcomes different from those of colonization or infection with oxacillin-sensitive strains.

Alterations in bacterial flora after large bowel surgery over the time of drainage

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Background This study analysed the bacterial flora colonizing drains after large bowel surgery with special regard to the qualitative changes of bacterial flora and to the dynamics of development of bacterial strain resistance.

Methods Forty-two patients who underwent large bowel surgery using a closed drainage system were examined. Specimens from each patient were taken three times: a smear from the peritoneal cavity during operation, a sample from the drain taken on day 3 after surgery and another sample from the drain at the end of drainage.

Results From 126 specimens, 159 aerobic and 59 anaerobic bacterial strains were cultured. Aerobes only were isolated from 62 specimens (49·2 per cent), mixed bacterial flora from 37 (29·4 per cent), and anaerobes only from nine (7·1 per cent). Eighteen specimens (14·3 per cent) gave no growth. The composition of bacterial isolates from patients was analysed. There was a significant decrease in the number of isolated anaerobic bacteria, from eight (19 per cent) to zero, and an increase in the number of aerobic bacteria, from 12 (29 per cent) to 30 (71 per cent) ($P < 0{\cdot}05$). During the three successive examinations there was an increased frequency of isolation of coagulase-negative staphylococci, from nine to 24 strains; and from eight to 16 and from none to three strains of *Enterococcus faecalis* and *Candida albicans* respectively. The number of cultured strains of *Escherichia coli* decreased from eight to one and of *Bacteroides* spp. from 24 to three. The frequency of isolation of methicillin-resistant coagulase-negative staphylococci increased significantly from one to 14 and the increase was clearly connected to the time of drainage and duration of hospital stay before operation. The same bacterial species were isolated twice or more often from 27 patients. More than one bacterial species were isolated from nine patients during two or three successive examinations. The sensitivity of the cultured bacterial species to antibiotics was tested; cephalosporins showed low activity against aerobic bacteria (20·1–28·1 per cent) and the resistance of *Enterococcus* spp. and *Staphylococcus* spp. was 90 and 50 per cent respectively.

Conclusion Prolonged drainage can cause retrograde infections, often related to environmental pathogens.

Antibiotic therapy in surgical intra-abdominal infection: piperacillin–tazobactam *versus* cefotaxime plus metronidazole – a multinational study

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Background Surgical intra-abdominal infection is a life-threatening condition requiring swift diagnosis, operative intervention and antimicrobial therapy. It results from disruption of the gastrointestinal tract in trauma and intra-abdominal disease. As culture data are not available initially, the antibiotic therapy has to be empirical and effective against the polymicrobial microflora, the great majority of which produce β-lactamase. This study compared the efficacy and safety of piperacillin, tagged to the β-lactamase inhibitor tazobactam, with the combination of cefotaxime and metronidazole in intra-abdominal infections.

Methods A randomized comparative multicentre study involving 364 patients with intra-abdominal infections requiring surgery was conducted by 23 centres in 11 countries. Patients received intravenously every 8 h either piperacillin 4 g with tazobactam 500 mg (P/T) or cefotaxime 2 g plus metronidazole 500 mg (C + M). Assessment of overall condition on entry into the study, and clinical and bacteriological responses at the end of treatment and follow-up were made.

Results Patients in the two groups were comparable in demographics, severity of disease, site of origin of the infection and operative intervention. Many patients had sustained trauma, including gunshot wounds and stab wounds. The overall mortality rate was 9·1 per cent ($n = 33$), 8·6 per cent in the P/T group ($n = 16$) and 9·5 per cent in the C + M group ($n = 17$). Death with sepsis occurred in 3·2 per cent ($n = 6$) of patients having P/T and 2·8 per cent ($n = 5$) of those receiving C + M. Clinical cure and improvement was evident in 94·8 and 90·4 per cent respectively ($P = 0{\cdot}22$). The bacterial response was satisfactory in 94·7 per cent of patients having P/T and 95·2 per cent of those receiving C + M (*P* not significant). Overall, both treatments were highly effective in microbial eradication. Adverse reactions, mainly nausea, vomiting, diarrhoea and rash, were comparable and minor.

Conclusion P/T is at least as effective and safe as C + M for the treatment of surgical intra-abdominal infection. It has the advantage of monotherapy, requiring less complex dosing schedules, which is important in busy surgical wards.

Use of teicoplanin and granulocyte colony stimulating factor in experimental methicillin-resistant *Staphylococcus aureus* pneumonia

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Background The effects of teicoplanin and/or granulocyte colony stimulating factor (G-CSF) on survival in an animal model of methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia were evaluated.

Methods Seventy-five male Swiss albino mice weighing 35 (range 32–43) g were used. Some 50 μl of a clinical isolate of MRSA (3×10^8 colony forming units per ml in saline solution) was administered by tracheal puncture in neutropenic mice. Neutropenia was achieved by using cyclophosphamide 200 mg per kg intraperitoneally. Mice were divided into five groups: group 1, tracheal puncture control in neutropenic mice ($n = 15$); group 2, pneumonia in neutropenic mice ($n = 15$); group 3, teicoplanin therapy for pneumonia in neutropenic mice ($n = 15$); group 4,

G-CSF therapy for pneumonia in neutropenic mice ($n = 15$); group 5, teicoplanin and G-CSF combined therapy for pneumonia in neutropenic mice ($n = 15$).
Results Teicoplanin therapy increased the survival rate ($P = 0{\cdot}0001$) whereas G-CSF therapy did not. Teicoplanin and G-CSF combined therapy improved the survival rate in comparison to that in groups 2, 3 and 4 ($P = 0{\cdot}0001$, $P = 0{\cdot}003$ and $P = 0{\cdot}0001$ respectively).
Conclusion Teicoplanin and G-CSF combined therapy seems effective in reducing mortality rates in MRSA pneumonia in experimental conditions.

Value of prophylactic antibiotic therapy in severe acute pancreatitis: unicentre prospective study

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Background Infected pancreatic necrosis (IPN) is the main cause of death in severe acute pancreatitis. The role of prophylactic antibiotic therapy in preventing infectious complications was investigated in a prospective clinical trial.
Methods Some 139 patients (86 men) with acute pancreatitis were admitted from November 1993 to September 1997; mean age was 55 (range 25–87) years. Severe acute pancreatitis was proven by contrast-enhanced computed tomography in 62 patients (45 per cent) with a varying extent of necrosis. The remaining 77 patients (55 per cent) suffered from mild or oedematous acute pancreatitis. All patients with severe acute pancreatitis ($n = 62$; mean Ranson score, Acute Physiology And Chronic Health Evaluation II score and C-reactive protein level at admission were 4·0 (range 1–10), 15·5 (range 6–28) and 191 (range 12–334) mg l^{-1} respectively) were transferred to the intensive care unit (ICU) and antibiotic therapy using intravenous imipenem–cilastatin was administered for 14 days at a dosage of 0·5 g three times daily. Fine-needle aspiration was undertaken for Gram staining and culture; a positive result was the indication for operative intervention.
Results Twenty-two (35 per cent) of 62 patients developed IPN after a mean of 27 (range 10–44) days and were operated on during the course of antibiotics. The following organisms were found: *Staphylococcus* spp. in 48 per cent, *Candida* in 38 per cent, *Enterococcus* spp. in 24 per cent, *Escherichia coli* in 19 per cent, *Klebsiella* spp. in 19 per cent and other bacteria in 24 per cent. In all other patients surgery was not indicated. ICU stay in patients with sterile necrosis was 6 (range 1–18) days and in those with IPN and operation 38 (range 3–152) days. The overall mortality rate in patients with severe acute pancreatitis was 6·5 per cent (four of 62); two of 40 patients with sterile necrosis died and two of 22 with IPN.
Conclusion This long-term therapy with imipenem–cilastatin in severe acute pancreatitis is effective in reducing the infection rate and delaying operation to the third week with optimal surgical conditions with an overall mortality rate below 10 per cent. However, further studies are necessary to determine the optimal length of antibiotic therapy and the risk of mycotic infection.

Effectiveness of an intervention programme in reducing postoperative infection and improving the quality and cost of antimicrobial use in a digestive surgical unit

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Background Since 1995, postoperative infections and surgical risk factors have been recorded continuously according to the Centers for Disease Control recommendations for infection control. Written protocols were defined in elective surgery, except for hernia surgery, according to the recommendations of the French Society of Anaesthesia and Intensive Care.
Methods In 1995, baseline infection rates were assessed in 1510 patients. In 1996, some modifications were made in antibiotic prophylaxis regimens, according to identified risk factors, and guidelines were defined in emergency, hernia and proctological surgery. Cefoxitin was preferred in colorectal surgery, and cefamandole was preferred in biliary and gastroduodenal surgery.
Results

Surgery	Wound infection rate (%)	Adequate antimicrobial prophylaxis (%)	Length of hospital stay (days)*	Benefit (days of hospital stay)
Colorectal				
1995 ($n = 327$)	24·8	88	15·6(10·1)	
1996 ($n = 322$)	19·3	96	14·9(7·2)	161
Gastroduodenal				
1995 ($n = 124$)	14·5	62	14·3(9·3)	
1996 ($n = 163$)	3·7	71	13·2(9·1)	163
Abdominal hernia				
1995 ($n = 91$)	24·2	—	13·2(9·5)	
1996 ($n = 122$)	9·8	76	10·5(4·8)	367

Values are mean(s.d.)

In 1996, a total of 1607 patients were recorded with an 11·1 per cent wound infection rate compared with 16·3 per cent in 1995 ($P < 0{\cdot}001$). Length of postoperative stay was reduced or equivalent. A benefit of at least 712 days of hospital stay was obtained with the most appropriate use of antimicrobial prophylaxis (*Table*). Guidelines for the use of antibiotics in therapy were distributed to surgeons and anaesthesiologists in 1995. Since July 1996, a restrictive policy to limit inadequate use of antibiotics has been in place. Physicians could prescribe all antibiotics. However, three levels (I, II, III) were distinguished, requiring approval of the infection control practitioner, respectively at day 7, 5 and 3 of the prescription. Analysis was made in terms of number of days of antibiotic treatment (DTAB = grams of antibiotics consumed divided by the defined daily dose). A significant reduction ($P < 0{\cdot}001$) of DTAB was observed during the last period. DTAB of quinolones dropped from 2741 days in 1995 to 1666 days in 1996, and DTAB of fluconazole dropped from 990 days in 1995 to 401 days in 1996, despite the comparable incidence of postoperative nosocomial infections. Consequently, the cost of the antibiotic treatment was reduced by 17·8 per cent in 1996 with comparable efficacy.
Conclusion Surgical units which are multidisciplinary could benefit by having infection control practitioners to reduce the cost of antimicrobial treatment.

Elution of six antibiotics bonded to Dacron vascular grafts sealed with three proteins: *in vitro* study

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Background The elution six antistaphylococcal antibiotics from vascular Dacron grafts sealed with albumin, collagen or gelatin was studied. The antibiotics tested were fusidic acid, pefloxacin, pristinamycin, rifampin, teicoplanin and vancomycin.
Methods The grafts were impregnated by simple soaking. The data were fitted to an exponential model and antibiotic half-lives ($t_{\frac{1}{2}}$) were calculated from the regression lines.
Results All the antibiotics tested were bound to the protein sealants. Antibiotic release varied with the type of antibiotic and the sealant. Rifampin was eluted most slowly, particularly with albumin- and gelatin-sealed grafts with a $t_{\frac{1}{2}}$ of 4–5 h and antibiotic activity still found at 48 h. The glycopeptides were also eluted slowly but there was no residual activity at 24 h.
Conclusion *In vitro* studies can be useful for evaluating antibiotic binding to protein-sealed grafts. It can be tested in animals or humans as local antimicrobial prophylaxis graft implantation in vascular surgery.

Bacteriology of multiple intra-abdominal fluid collections in acute pancreatitis

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Background The complicated form of acute pancreatitis frequently produces multiple necrotic foci in the pancreas and fatty tissues in the peripancreatic spaces. Secondary infection of these foci is an important prognostic factor for these patients. Surgical intervention and effective adjuvant antibiotic treatment can decrease infection-related complications and reduce the mortality rate. The antibiotic therapy selected at the time of initial intervention should cover aerobic and anaerobic bacteria. Refinement of antibiotic coverage should be based on the culture result of samples obtained at operation.

Methods A prospective study was performed during 1995–1996 to investigate the pathogens in multiple abscesses and fluid collections in patients operated on for infected pancreatic necrosis.

Results Some 171 samples were collected during 76 operations on 69 patients and analysed bacteriologically. The mean number of samples per patient was 2·1. The cultures were positive in 159 cases (93 per cent) and negative in 12 cases (7 per cent). Fifty-six different species were cultured, of which 17 were Gram-negative (mainly Enterobacteriaceae), 19 Gram-positive (mostly enterococci) and 19 anaerobes. The pathogens were the same in each sample in 13 interventions (17 per cent), and were different (either the species or the sensitivity of isolates) at 63 operations (83 per cent). It has been shown that separate fluid collections could be infected with various pathogens.

Conclusion These data suggest that the anti-infective therapy of these patients should be based on the results of multiple samples taken during operation.

Oral ofloxacin in perioperative prophylaxis in abdominal surgery

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Background Antibiotic prophylaxis in abdominal surgery is recommended in patients with colonic resection or in patients undergoing extensive surgery. In aseptic surgery antibiotic prophylaxis is reserved for patients with a high infection risk. In a prospective study serum and tissue concentrations of oral ofloxacin were measured in order to provide a pharmacokinetic basis for oral prophylaxis.

Patients Patients were given ofloxacin 400 mg orally 2 h before surgery. Plasma and tissue concentrations of ofloxacin were measured by high-pressure liquid chromatography. Patients were divided into a low-risk group (ten patients having inguinal hernia repair and ten patients undergoing cholecystectomy) and a high-risk group (ten patients undergoing colonic resection and ten pancreatic resection).

Results Ofloxacin was administered a median of 145 (range 70–315) min before surgery. The median time for the surgical procedure was 170 (range 25–510) min. Median ofloxacin serum level at the beginning of the operation was 3·2 (interquartile range 2·6–4·4) mg l^{-1} and at the end of surgery 2·7 (1·8–3·5) mg l^{-1}. Tissue concentrations are listed in the *Table*.

Ofloxacin	Hernial sac	Gallbladder	Colon	Pancreas
Tissue concentration (mg l^{-1})	2·7 (1·7–3·6)	7·9 (4·9–12·3)	5·1 (4·6–7·3)	6·6 (3·8–7·1)
Tissue : serum ratio	1·1 (0·5–1·3)	2·8 (1·4–3·8)	1·9 (1·5–2·2)	2·6 (1·7–5·0)

Values are median (interquartile range)

The half-life of ofloxacin was median 305 min, total clearance 188 ml min^{-1} and volume of distribution 117 litres. Oral ofloxacin achieves high serum and tissue concentrations throughout surgical procedures where administered 2 h before operation.

Conclusion Pharmacokinetic data show that perioperative prophylaxis with oral ofloxacin is a low-cost alternative to intravenous prophylaxis. The effectiveness of oral prophylaxis should be investigated in controlled studies.

Translocation of different strains of enteric bacteria in an *ex vivo* model

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Background Passage of enteric bacteria through the intact intestinal mucosa is an initial step in the pathogenesis of abdominal sepsis. In this study, the ability of different enteric bacterial species to cross the intact colonic mucosa was examined in an *ex vivo* model.

Methods The colon of 15 male Wistar rats was removed; the colonic mucosa was dissected free and placed in a modified Ussing system consisting of eight chambers. The mucosal reservoir of each chamber was filled with 2 ml of a suspension of bacteria (concentration ranging from $3{\cdot}8 \times 10^7$ to $5{\cdot}8 \times 10^8$ colony forming units (c.f.u.) per ml) in Dulbecco's Modified Eagle Medium (DMEM), whereas the serosal side was filled with sterile DMEM. Samples were drawn from the serosal side at 0, 1, 2, 3 and 4 h after the start of the experiment and plated on agar plates allowing selective growth. After 18 h of incubation, c.f.u. were counted. Concentrations of more than 100 c.f.u. ml^{-1} on the serosal side were considered positive for translocation. The following bacterial strains were investigated: *Enterococcus faecalis* OG1X, *E. faecalis* OG1X:pAM721, *E. faecalis* INY 3000, *Salmonella typhimurium* ATCC BV VI and *Escherichia coli* Hb 101.

Results Within 4 h, *S. typhimurium* was detected on the serosal side in 12 of 15 experimental settings. None of the three strains of enterococci nor *E. coli* Hb 101 was found positive for translocation (*E. faecalis* OGIX, seven experiments; *E. faecalis* OG1X:pAM721, seven experiments; *E. faecalis* INY 3000, eight experiments; *E. coli* Hb 101, 13 experiments).

Conclusion These results show that bacterial translocation is a species-dependent process. *S. typhimurium* ATCC BV VI is able to translocate across intact rat colonic epithelium within 4 h whereas the enterococci tested as well as *E. coli* Hb 101 are not. The results are consistent with the clinical observation that infections with enterococci occur in the later phase of abdominal sepsis.

Stroke volume *versus* cardiac output as a marker for predicting postoperative morbidity

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Background A significant peroperative tissue oxygen debt appears to predispose to subsequent complications including organ dysfunction. Whether this can be detected in the immediate postoperative period by using either absolute levels or trends in stroke volume (SV) and cardiac output (CO) remains to be ascertained. This study investigated whether non-invasive monitoring of SV and CO by oesophageal Doppler ultrasonography could be used as prognostic parameters in patients undergoing cardiac surgery.

Methods Twenty patients admitted to the intensive care unit following cardiac surgery, and apparently haemodynamically stable, were enrolled. An oesophageal ultrasound probe (ODM 2; Abbott, UK) was inserted for measurement of SV and CO. These and routine haemodynamic variables (mean arterial pressure (MAP), central venous pressure (CVP), heart rate

(HR), arterial base deficit (sBE), urine output and core–toe temperature difference) were recorded. Forty per cent underwent emergency coronary artery bypass grafting (CABG) and 60 per cent routine CABG and/or valve replacement. Nine patients developed postoperative complications and two died.
Results Significant differences ($P<0{\cdot}05$) were seen between complicated and uncomplicated cases for SV, sBE and HR at admission, but not for CO. The area under the receiver–operator characteristic curve was significantly higher for SV than for HR or sBE ($P<0{\cdot}01$). The risk of morbidity after cardiac surgery was significantly related to low SV, high HR and raised sBE but not to CO. A compensatory tachycardia maintains CO in apparently haemodynamically stable patients. It may be postulated that a low SV (secondary to hypovolaemia or poor myocardial function) plus additional sympathetic stimulation may be injurious. This process can best be monitored by measuring SV.
Conclusion SV is a useful marker for morbidity after cardiac surgery.

Diffuse peritonitis in an obstetric and gynaecological intensive care unit: causes and treatment

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Background Causes and treatment of diffuse peritonitis in an obstetric and gynaecological intensive care unit were examined.
Methods During a 2-year period in this intensive care unit 17 patients with diffuse peritonitis of different origin were treated. Most of them (11) had a pre-existing tubo-ovarian abscess; there were also cases of tubo-ovarian abscess and appendicitis (two patients), tubo-ovarian abscess and paralytic ileus, infection after caesarian section, subtotal abdominal hysterectomy and vaginal hysterectomy. The mean age of the patients was 44 (range 18–68) years. Surgical treatment was performed when indicated and 22 operative procedures were undertaken. Most frequently performed were total abdominal hysterectomy with bilateral adnexectomy in eight of the 17 patients and adnexectomy in three patients. Other surgical procedures included appendicectomy, intestinal resection, hysterectomy with conservation of the ovaries, salpingectomy, resection of the ovaries and extirpation of an abscess capsule. In all cases adhesiolysis and drainage was performed.
Results Purulent material obtained from the operative field after microbiological analysis presented various bacterial flora, with a predominance of *Escherichia coli* (25 per cent), *Streptococcus α haemolyticus*, *Pseudomonas* spp., *Acinetobacter*, *Staphylococcus aureus* and *Staphylococcus epidermidis* (10 per cent), *Streptococcus β haemolyticus*, *Bacteroides* spp., *Enterococcus*, *Klebsiella* and anaerobic bacilli (5 per cent). High doses of broad-spectrum antibiotics were given during the postoperative period. All of these patients were discharged from the hospital except one with a pulmonary embolus.
Conclusion Diffuse peritonitis is a relatively rare but severe condition in obstetric and gynaecological practice. With removal of infective foci and adequate antibiotic therapy most cases of severe inflammatory disease can be cured.

Antibiotic resistance of pathogens cultured from multiple intra-abdominal fluid collections

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Background The bacteriology and antibiotic resistance of infective agents in multiple intra-abdominal fluid collections and abscesses due to necrosis of pancreas were studied prospectively.
Methods A total of 171 samples representing different fluid collections and abscesses were taken from 69 patients at 76 operations (2·1 samples per patient).
Results Enterobacteria were the most frequent pathogens, and were present in 40·7 per cent of 329 isolates belonging to 56 species, but the predominance of *Escherichia coli* was not significant (*E. coli* 13 per cent, *Bacteroides* spp. 11 per cent, *Enterococcus* spp. 11 per cent, *Klebsiella* spp. 10 per cent, *Pseudomonas aeruginosa* 10 per cent, *Enterobacter* spp. 8 per cent, *Streptococcus* spp. 7 per cent). Resistance rates were analysed for antibiotics that were used widely for the treatment of patients with infected necrosis of the pancreas. Ceftazidime resistance was frequent among Gram-negative bacteria: *E. coli* 7 per cent, *Klebsiella* spp. 24 per cent, *Enterobacter* spp. 58 per cent, *Citrobacter* spp. 50 per cent, *P. aeruginosa* 9 per cent. In contrast, imipenem resistance occurred only in *Enterobacter* spp. (8 per cent) and in *P. aeruginosa* (10 per cent) of the Gram-negative organisms. Ciprofloxacin showed no activity against 6–42 per cent of enterobacteria and 28 per cent of *P. aeruginosa*. Amikacin resistance rates ranged from 3 per cent (*E. coli*, *P. aeruginosa*) to 27 per cent (*Enterobacter* spp.), while gentamicin frequently proved ineffective. Ampicillin and high-level gentamicin resistance occurred frequently among enterococci (30 and 66 per cent respectively), but only two of 33 isolates were vancomycin resistant. Cefoxitin was the least active antianaerobic agent.
Conclusion The high resistance rates suggest that the nosocomial pathogens play an important role in the superinfection of necrotic pancreatic tissues. Consequently, antibiotic therapy should be based on the bacteriological results obtained from representative, multiple, peroperative specimens.

Pathophysiological parameters of knee-joint effusions in the absence and presence of infection

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Background The metabolic activity of bacterial pathogens and host defence activity may often alter milieu factors, such as pH, partial pressure of oxygen P_{O_2} and partial pressure of carbon dioxide P_{CO_2} at the site of infection. Studies performed in peritoneal fluid revealed significant differences in these variables between infected and non-infected specimens. Furthermore, altered milieu factors are known to influence antibiotic activity. To verify such observations in joints, 56 samples of knee-joint effusions were analysed.
Methods Patients over 18 years of age suffering from knee-joint effusions were enrolled. Effusions were sampled immediately before arthroscopic or other operative procedures for diagnostic as well as therapeutic reasons. The measurements were completed within 5 min after sampling using a radiometer ABL 505. Knee-joint effusions from 28 men and 28 women (mean age 57 (range 18–90) years) were investigated. The following diagnoses were established: osteoarthritis (31), recent trauma (17), cartilage disorders (three) and infections (five).
Results Significant differences were observed in the absence or presence of infection (mean (range)): pH, 7·3 (7·0–7·5) *versus* 6·9 (6·7–7·0); P_{O_2}, 17·6 (2·8–21·6) *versus* 8·8 (4·3–12·1) kPa; and P_{CO_2}, 6·4 (1·2–12·6) *versus* 13·4 (6·4–17·4) kPa respectively. No differences were observed in pH, P_{O_2} and P_{CO_2} between 17 acute trauma lesions and 34 chronic lesions. The conditions prevailing within knee joints reflect data documented in the abdomen in the absence or presence of infection. Using the threshold values predictive for infection in the abdomen (pH less than 7·1, P_{O_2} less than 6·5 kPa and P_{CO_2} greater than 8 kPa) the following sensitivities and specificities indicating the presence of bacterial knee infection were obtained: pH 100 and 96 per cent; P_{O_2} 60 and 84 per cent; P_{CO_2} 100 and 94 per cent.
Conclusion Data on *in vivo* conditions may be helpful in designing more predictive *in vitro* tests of antimicrobial activity to guide antibiotic treatment of joint infections. In addition, rapid assessment of these pathophysiological variables might be useful for clinical decision making.

Relaparotomy in peritonitis: characterization and outcome of patients with persisting abdominal sepsis

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Background The characteristics and outcome of patients with persisting abdominal sepsis were evaluated.

Methods Some 105 consecutive patients treated from 1986 to 1996, in whom standard surgical treatment of secondary peritonitis failed, were reviewed retrospectively.

Results The mean(s.d.) Acute Physiology And Chronic Health Evaluation (APACHE) II score at the beginning of treatment was 20·7(9·1). Preoperative severe organ failure measured by the GORIS score had a significant impact on survival. A significantly adverse outcome was found in patients older than 70 years ($P = 0·002$), with a duration of illness greater than 24 h ($P = 0·0001$), with a serum albumin level less than 30 g l^{-1} ($P = 0·0001$) and with thrombocytopenia below 60×10^9 per litre ($P = 0·02$). Re-exploration performed more than 48 h after the initial operation resulted in a significantly higher mortality rate (76·5 per cent; $P = 0·0001$). However, the lowest mortality rate (18 per cent) was observed in patients who underwent reoperation on demand within 48 h. The APACHE II scores differed, although not significantly, in all four categories of patients (early and late, planned and relaparotomy on demand). Postoperative organ failure in more than four organ systems with a GORIS score of 9 or more was associated with a mortality rate of 93 per cent. In patients with a GORIS score of 5–8, multiple organ system failure (MOSF) for up to 6 days led to a significantly worse outcome ($P = 0·01$). High-risk patients with diffuse peritonitis require timely and frequent reoperations.

Conclusion These data show that planned and on-demand relaparotomy lead to similar results. However, the decision to perform a relaparotomy on demand must be made within 48 h after the initial operation, at least before MOSF emerges. Better intensive care may help the patient to survive severe MOSF of up to four organ systems. Supporting vital functions over a longer period has been effective in reducing the traditionally high mortality rate in these patients.

Effects of lipopolysaccharide and antibiotics on protein synthesis in muscle and intra-abdominal organs

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Background Intestinal barrier function is suggested to be of increased importance during catabolic states such as trauma and sepsis. Changes in protein synthesis in intra-abdominal tissues during sepsis or after antibiotic therapy are not clear. This study examined changes in protein synthesis rates in muscle and intra-abdominal organs after lipopolysaccharide (LPS) administration and during antibiotic therapy in mice.

Methods In the first part of the study non-fasting Swiss Webster mice received an intraperitoneal injection of LPS or saline. After 230 min a flooding dose of L-[^{2}H5]phenylalanine was injected intravenously. Some 10 min later the animals were killed, blood was collected and tissues were sampled. Protein synthesis rates were measured by the incorporation of injected L-[^{2}H5]phenylalanine into tissue proteins using GCMS. In the second part of the study mice were given either a mixture of streptomycin 2 mg ml^{-1} and bacitracin 2 mg ml^{-1} in their drinking water, or water only together with standard chow. After 3 days a flooding dose of L-[^{2}H5]phenylalanine was injected intravenously and samples were taken in the same way after 10 min.

Results Four hours after LPS, protein synthesis rates (k_s) decreased in all tissues examined (skeletal muscle, spleen, liver, enterocytes, mesenteric lymph nodes (MLNs) and Peyer's patches) by 30–60 per cent ($P < 0·01$). After oral antibiotic treatment k_s decreased in heart, colon and MLNs by 10–20 per cent ($P < 0·01$).

Conclusion After LPS injection, protein synthesis was reduced in all tissues, including intestine and lymphoid tissue. After antibiotic treatment a reduction was seen in heart, colon and MLN protein synthesis, possibly due to disturbed intestinal flora. These effects might be of importance as they may damage intestinal barrier function in septic states.

Peritoneal activation and severity of disease in human peritonitis

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Background The severity of peritonitis can be described clinically by the use of several scoring systems. However, the activation of peritoneal cells has not been included in the grading of peritonitis. This study evaluated the cellular activation of the inflamed human peritoneum and determined possible relations between cellular activation and clinical scores.

Methods In nine patients with diffuse peritonitis, peritoneal specimens were taken at the beginning of intervention. Monocyte–macrophage activity was assessed immunohistochemically using antibodies against macrophage inhibiting factor-related proteins (MRPs) 8 and 14. The antibody clone HAM 56 was used to identify local macrophages. Cellular expression of interleukin (IL) 1 was also measured. All examinations were performed in paraffin sections using the avidin–biotin complex technique. Evaluation of the clinical state was done by using the Mannheim Peritonitis Index (MPI), Peritonitis Index Altona II (PIA II) and Acute Physiology Score (APS). C-reactive protein (CRP) levels were measured before operation in serum.

Results The expression of MRP-8 and MRP-14 showed a focally increased to diffuse dense interstitial staining. Activation corresponded to high CRP values (median 22·0 (range 4·7–42·6) mg dl^{-1}). Resident peritoneal macrophages (HAM 56) showed a relatively slight increase. IL-1 expression was discrete and in some cases not detectable. Activation was independent of MPI (median 30 (range 21–39)), PIA II (+0·57 (−1·64 to +1·79)) and APS (2 (range 1–19)).

Conclusion The pattern of peritoneal inflammatory reactions is relatively uniform and does not correspond to the clinical grading of severity. The surprisingly low expression of IL-1 may reflect downregulation after presumed early increase during the course of peritonitis.

Experimental studies of biliary piperacillin excretion

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Background Piperacillin is a β-lactam antibiotic with broad-spectrum activity against Enterobacteriaceae, enterococci and anaerobes. Its activity, along with high reported biliary levels, has prompted its clinical use in treating biliary infections. A number of organic anions are known to decrease biliary secretion of cholesterol and phospholipid without affecting bile acid secretion. The purpose of the present study was to examine the possible uncoupling effects of different doses of piperacillin on biliary lipid secretion in rats.

Methods Male Wistar rats weighing 250–300 g were injected intravenously with piperacillin at four different doses: 0·3, 1, 2 and 3 nmol per kg body-weight, and bile samples were collected for a total of 2 h. Bile acid, cholesterol and phospholipid concentrations were measured in bile by commercially available enzymatic methods. The bile lithogenic index (i.e. percentage cholesterol saturation) was calculated by the method of Hoffman (1973).

Results Piperacillin administration inhibited bile acid, cholesterol and phospholipid secretion at all doses tested. The cholesterol:bile acid and cholesterol:phospholipid ratios were increased significantly. The phospholipid:bile acid ratio was reduced significantly. The lithogenic index of bile was significantly increased at all doses (+175, +103, +81 and +150 per cent respectively).

Conclusion These data indicate that piperacillin induces a marked reduction in bile acid, cholesterol and phospholipid biliary secretion. This effect gives rise to a greater cholesterol saturation in bile which represents a major factor for cholesterol gallstone formation.

Re-evaluation of empirical antibiotic therapy

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Background Important complications after surgery are surgical infections for which empirical antibiotic therapy is required. To establish precise antibiotic therapy, the microbiological spectrum and sensitivity must be determined. This study examined whether new antibiotics have produced qualitative changes in microbial flora isolated from patients and determined possible modifications in sensitivity.

Methods Some 7414 samples, obtained from 6236 patients operated on by the authors during the past 6 years, were analysed retrospectively. The frequency of isolation of the most common organisms was determined and changes in sensitivity after different antibiotics were evaluated.

Results A significant global change was found ($P = 0{\cdot}0008$) in surgical bacteriology responsible for infection, with a significant reduction ($P = 0{\cdot}006$) in *Staphylococcus aureus* and an increase in *Staphylococcus epidermidis* ($P = 0{\cdot}026$). An increase in the isolation of fungi was also observed ($P = 0{\cdot}00006$). Modifications in the incidence of *Escherichia coli*, *Pseudomonas aeruginosa* and *Streptococcus faecalis* were not confirmed. Changes in sensitivity were not observed, with the exception of *P. aeruginosa*, which showed a decrease in sensitivity to piperacillin ($P = 0{\cdot}0033$), although a sensitivity of 100 per cent was associated with tazobactam, and sensitivity to ceftazidime and amikacin was maintained at 100 per cent. A decrease in sensitivity to cefotaxime of between 75 and 39 per cent ($P = 0{\cdot}014$) was observed and to gentamicin of between 100 and 76 per cent, while sensitivity to tobramycin was maintained at over 90 per cent. *P. aeruginosa* presented over 90 per cent resistance to amoxycillin–clavulanic acid, which is a widely used antibiotic in these wards. Finally, non-urinary *E. coli* showed changes in sensitivity to cephazolin ($P = 0{\cdot}000001$).

Conclusion A decrease in *S. aureus*, as responsible for surgical infections, has occurred with a progressive increase in *S. epidermidis* and fungi. With the exception of *P. aeruginosa* and non-urinary *E. coli*, no changes in sensitivity were observed. It is useful periodically to evaluate the frequency of isolated organisms and sensitivity to establish a typical flora in each department and to evaluate the need to modify antibiotic therapy.

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Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses

Sir

I read with interest the article by Koch *et al.* (*Br J Surg* 1997; **84**: 750–9) in which unfractionated heparin was compared with low molecular weight heparin (LMWH) in the prevention of postoperative deep vein thrombosis (DVT).

In a subgroup analysis the authors conclude that in general surgery a high dose of LMWH is not more effective than a low dose and that the low dose is a more promising concept. The authors state that the results of a large clinical trial would be more reliable than the results from a meta-analysis; there is such a study[1] that the authors may have missed. This is difficult to understand as data were collected from pharmaceutical companies and Medline until March 1996. The sample size calculation in this prospective double-blind randomized multicentre study was made to allow an analysis of the prophylactic effect and safety in patients undergoing elective surgery for abdominal malignancy. The results (frequency given as percentage) in the 1303 patients was as follows:

	Dose of Dalteparin		95 per cent confidence interval of differences
	2500 units	5000 units	
DVT* (intention to treat) ($n = 1303$)	14·9	8·5	2·1 to 8·9
DVT* (correct prophylaxis) ($n = 1154$)	15·1	8·8	2·1 to 9·4
Haemorrhagic complication	3·6	4·6	−2·8 to 1·4

*Deep vein thrombosis (DVT) diagnosed by fibrinogen uptake test

Meta-analysis is a valuable scientific instrument with advantages and disadvantages, but large properly performed controlled trials are the gold standard to evaluate the efficacy of clinical interventions. This view is strongly supported by recent data from a comparison between results in meta-analysis and randomized controlled trials on the same topic[2]. The dose comparison made by Koch *et al.* shows that these are important factors influencing the results of clinical studies but not taken into account in a meta-analysis. In this case such factors could be differences in patient population and time of first dose.

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1 Bergqvist D, Burmark US, Flordal PA, Frisell J, Hallböök T, Hedberg M *et al.* Low molecular weight heparin started before surgery as prophylaxis against deep vein thrombosis: 2500 *versus* 5000 XaI units in 2070 patients. *Br J Surg* 1995; **82**: 496–501.
2 LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med* 1997; **337**: 536–42.

Author's reply

Sir

We welcome the comment by Dr Bergqvist and the opportunity to reply. Our meta-analysis was intended to resolve the question of whether LMWH can replace unfractionated heparin (UFH) under certain circumstances and therefore did not include the study of Bergqvist *et al.*[1]. This study investigates another question (randomized and double-blind comparison to assess a dose–response effect). This has correctly been termed the gold standard for treatment comparisons and our results can, at best, add some additional evidence. Dr Bergqvist's conclusion from our meta-analysis that low-dose LMWH is superior to high-dose LMWH is based on an indirect comparison which, in our opinion, exceeds what can be achieved in a publication based meta-analysis[2].

We agree that (even for the comparison of LMWH and UFH) many questions remain unresolved[3]. Treatment effects may differ in high- and low-risk patients (as is indicated by Dr Bergqvist's results), the role of mechanical methods in thrombosis prophylaxis needs investigation and additional information on commencement of treatment before and after surgery is necessary.

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1 Bergqvist D, Burmark US, Flordal P, Frisell J, Hallböök T, Hedberg M *et al.* Low molecular weight heparin started before surgery as prophylaxis against deep vein thrombosis: 2500 *versus* 5000 XaI units in 2070 patients. *Br J Surg* 1995; **82**: 496–501.
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Effect of a no-conversion policy on patient outcome following laparoscopic cholecystectomy

Sir

We read with interest the paper by Wallace and O'Dwyer (*Br J Surg* 1997; **84**: 1680–2) but were surprised at its main conclusions. The authors state that one of the potential drawbacks of laparoscopic cholecystectomy is lack of experience with the open procedure. Advocacy of a no-conversion policy will further restrict an already diminishing experience with open cholecystectomy with implications for surgical trainees.

We believe it to be unwise to suggest that surgeons should not convert to an open procedure. Those with less experience than Mr O'Dwyer might be tempted not to convert with potentially significant complications. The authors compared an early with a more recent experience and outlined the reasons for conversion in the first 127 procedures. No information is given concerning the number of patients in the more recent series with previous abdominal surgery, intraoperative difficulties in identifying biliary anatomy or haemorrhage. Are these groups strictly comparable?

Between July 1990 and December 1997, 896 laparoscopic cholecystectomies were performed in our unit, of which 75 were converted to an open procedure (8·4 per cent). Indications for conversion included anatomical uncertainty or adhesions from previous surgery ($n = 48$), empyema ($n = 14$), bleeding ($n = 4$) and technical problems ($n = 4$). We do not believe that it is always possible to be certain of biliary anatomy during laparoscopy. Conversion should be undertaken in this circumstance, as the risks of open cholecystectomy are less than those associated with laparoscopic bile duct injury. In our experience learning curves or better laparoscopic instruments do not diminish the need for open cholecystectomy in a small percentage of patients. These patients, by the nature of their disease, demand even more experienced surgical technique.

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Author's reply

Sir
We are grateful to Mr Barry and colleagues for their comments but they appear to confuse one of our introductory statements, that one of the potential drawbacks of laparoscopic cholecystectomy is lack of experience with open cholecystectomy, with our only conclusion that a no-conversion policy can be adopted for laparoscopic cholecystectomy without adversely affecting patient outcome. There was no difference between the patients in both groups in our study with respect to previous abdominal surgery, severity of disease etc. We know of no published series where conversion rates have not diminished with experience and it will not always be possible to demonstrate the anatomy at open cholecystectomy and the risk of serious bile duct injury may be no less than that at laparoscopic cholecystectomy. In the small percentage of patients where laparoscopic cholecystectomy is not feasible, and this should be 1–2 per cent of patients rather than the 8 per cent suggested by Barry *et al.*, we believe cholecystectomy, with complete stone removal, may be the safest procedure.

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Magnetic resonance imaging in evaluation of the common bile duct

Sir
The clinical role of magnetic resonance cholangiopancreatography (MRCP) and how the algorithm proposed by Musella *et al.* (*Br J Surg* 1998; **85**: 16–19) may fit into routine clinical practice remains unclear. The main criticism of MRCP, when compared with endoscopic retrograde cholangiopancreatography (ERCP), has been that no therapeutic option can be offered when diagnostic information is obtained[1]. The authors suggest routine MRCP for patients with symptomatic common bile duct (CBD) involvement (jaundice, evident biochemical abnormality and dilated ducts on ultrasonography). ERCP is usually necessary in many of these patients as a therapeutic procedure either for sphincterotomy and stone removal or for temporary or permanent stenting in the event of benign or malignant stricture. In their series nine of 11 patients in this category underwent subsequent ERCP and sphincterotomy. MRCP may only add further to the cost of diagnostic investigation in these patients without providing any additional benefit or information.

The potential clinical application of MRCP may be in the following circumstances: (1) patients who require purely diagnostic ERCP examination; (2) after unsuccessful ERCP; (3) when technical difficulties of ERCP can be anticipated; and (4) for evaluation of the biliary tree in patients with mild biochemical or ultrasonographic signs of CBD involvement before laparoscopic cholecystectomy[2].

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1 McDermott VG, Nelson RC. MR cholangiopancreatography: efficacy of three dimensional turbo spin-echo technique. *AJR Am J Roentgenol* 1995; **165**: 301–2 (Letter).
2 Soto JA, Yucel EK, Barish MA, Chuttani R, Ferrucci JT. MR cholangiopancreatography after unsuccessful or incomplete ERCP. *Radiology* 1996; **199**: 91–8.

Author's reply

Sir
The main criticism you level against MRCP in patients symptomatic for involvement is that it adds costs without providing any additional information. Allow us to disagree with you for the following reasons.

First, the most frequent causes of 'surgical' jaundice remain CBD stones or periampullary and pancreatic head carcinoma. The purpose of the study on symptomatic patients was to demonstrate that MRCP and ERCP in such patients had the same efficacy. Many authors[1,2] do not suggest diagnostic ERCP in symptomatic patients when a periampullary or pancreatic malignancy is suspected. In such patients an assessment of mass extension and resectability by the combined use of MRCP and helical computed tomography is to be preferred. ERCP will be useful for non-resectable lesions when a stenting procedure is required. On the other hand if stones are seen at MRCP, we prefer to drain the CBD by endoscopic sphincterotomy, as suggested in the algorithm. Others[3], who want to preserve sphincter function, will attend to choledocholithiasis at the time of laparoscopic cholecystectomy. ERCP is not the only therapeutic option to treat CBD stones; it is an invasive diagnostic approach that should be performed only when an operative procedure (sphincterotomy, stenting) is required on the basis of a previous non-invasive evaluation.

Second, the same authors[4] cited by Mr Sudhindran, in a newer series, have enlarged their indication to perform MRCP. It may decrease significantly the need for purely diagnostic ERCP, and is therefore recommended in the routine diagnosis of biliary tract disease.

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Prognostic factors in a series of 297 patients with gastric adenocarcinoma undergoing surgical resection

Sir

I was interested to read the paper by Sánchez-Bueno *et al.* (*Br J Surg* 1998; **85**: 255–60) describing prognostic factors in patients who had undergone surgical resection for gastric carcinoma. Clinical, treatment-related and anatomicopathological variables were analysed but no mention was made of variables relating to tumour biology. Recent reports have described components of the plasminogen activating system as new factors that are also associated with poor prognosis.

Urokinase plasminogen activator and its inhibitor PAI-1, determined by semiquantitative immunohistochemistry[1,2] or by enzyme-linked immunoassay[3–5], were shown to be independent prognostic parameters for short survival, particularly in patients with diffuse-type tumours by the Laurén classification. Heiss *et al.*[6] showed that the expression of the urokinase plasminogen activator receptor on disseminated tumour cells in bone marrow aspirates taken at the time of surgery from patients with gastric carcinoma predicts early relapse and is an independent prognostic variable.

The urokinase plasminogen activator system is thought to have an important role in the cellular mechanisms that result in invasion and metastasis[7]. It is interesting to note that in the multivariate analysis performed by the authors two of the four independent variables, penetration depth of gastric wall and lymph node involvement, are the consequences of these processes. Measurement of components of this system in patients with gastric carcinoma provides additional prognostic information which may be useful in planning treatment.

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Pilonidal sinus: experience with the Karydakis flap

Sir

I thank Dr Kitchen (*Br J Surg* 1996; **83**: 1452–5) and Schoeller *et al.*[1] for their contributions to pilonidal disease. Dr Kitchen's symmetrical flap excision is an important refinement. Both authors properly emphasize the importance of creating a shallow cleft and placing the final suture lines away from a deep midline.

Which operation is simplest? Muscle transfers are unnecessary as the authors point out. Shifting of fascia and fat is also unnecessary. The goal is to reshape dermis and epidermis and, therefore, skin alone needs to be moved[2]. Experience shows that fat falls into place and heals beneath intact skin.

A chronic abscess wall is a victim to be protected. Its cells are striving to heal in a choking cloud of anaerobic bacteria which flood in from their breeding place in the airless cleft. The embattled fat is not a villain to be cut away as the 'total excision to periosteum' as conventional texts instruct. Such instructions are based on a faulty concept of the deformed tissues as generator, not sufferer, of disease. Freed of the noxious infusion from a damp cleft, deep tissues will always heal[3]. Total excision hospitalized 79 000 servicemen for an average of 55 days in World War II and was abandoned.

Shallow clefts and ventilated suture lines solve every pilonidal problem unresponsive to conservative treatment if excision of the rare epithelial tube is included. In the search for the simplest effective operation, shifting skin alone as a day-surgery procedure has much to recommend it.

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Topical glyceryl trinitrate cream for anal fissure

Sir

Glyceryl trinitrate (GTN) cream has recently been advocated as an effective treatment for anal fissure[1]. Apart from headache it appears to produce few complications but two recent patients highlight the pitfalls of its widespread indiscriminate use.

Patient 1. A 43-year-old man presented to his general practitioner (GP) with a 3-month history of perianal pain aggravated by defaecation with increased mucus production and traces of bright red blood on defaecation. Intense sphincteric spasm prevented digital rectal examination. He was given topical 0·2 per cent GTN cream for 1 month. Despite slight improvement significant symptoms persisted and he was referred to a colorectal surgeon. Intense sphincteric spasm made examination impossible. Examination under anaesthesia revealed a low rectal carcinoma. He received preoperative radiotherapy followed by a low anterior resection with a colonic J pouch.

Patient 2. A 49-year-old man presented to his GP with fresh rectal bleeding and pain on defaecation. He had anal spasm and an oedematous skin tag. GTN cream (0·2 per cent) was applied for 2 months with no success. When referred to the surgical department a squamous cell carcinoma of the anal canal was found which was treated by chemoradiation.

Edwards *et al.*[2] demonstrated that patients with anal carcinoma are often given a benign diagnosis before the true nature of the disease is established and others have suggested that this may adversely affect prognosis[3]. These patients illustrate the importance of excluding more serious conditions before relying on topical GTN. The option of treating anal fissure without operation does not reduce the need for full examination, if necessary under anaesthesia.

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Long-term oral administration of branched chain amino acids after curative resection of hepatocellular carcinoma: a prospective randomized trial

Sir
I read with interest the report from the San-In Group of Liver Surgery promoting the benefits of branched chain amino acids (BCAAs) after liver resection for hepatocellular carcinoma (*Br J Surg* 1997; **84**: 1525–31). The authors suggest that prolonged oral intake of a proprietary feeding solution rich in BCAAs (Aminoleban EN, Otsuka Pharmaceutical Company, Tokyo, Japan) may be of benefit in improving clinical and biochemical recovery after hepatectomy in patients with underlying liver disease. Unfortunately, this interpretation is not supported by the data. The study design is seriously flawed due to the lack of a control group with supervised intake of an isonitrogenous, isocaloric feeding supplement. While the treatment group was given 100 g of the test formulation per day (containing 27 g protein, 62 g dextrin and 7 g rice oil, and providing 420 kcal) in addition to normal diet for 1 year, the control group 'ate their usual meals'.

It is widely accepted that in patients with chronic liver disease impaired dietary intake is one of the principal causes of nutritional deficiency (although absorptive and metabolic derangements may also contribute)[1]. Furthermore, the role of BCAA feeding formulas in this group of patients is far from clear, with studies providing conflicting results and demonstrating uncertain benefit[2]. There is evidence that conventional protein and casein preparations produce comparable results to BCAA solutions when given over prolonged periods[3]. I suggest that the benefit demonstrated in the study by the San-In group can be explained largely by the overall effect of improved protein calorie intake, rather than any specific effect mediated by BCAAs. In this regard, the recent clinical guidelines issued by the American Society for Parenteral and Enteral Nutrition recommend that BCAA-enriched formulas be reserved for patients with established encephalopathy in whom standard medical care has failed and adequate protein intake cannot otherwise be tolerated[4]. While the search for therapies to improve recovery (and liver regeneration) after hepatectomy in patients with cirrhosis continues, it is important that future attempts to evaluate specific nutritional strategies should have an appropriate isonitrogenous, isocaloric control arm. Improperly controlled studies simply add further confusion to a clinical problem replete with unproven (feeding) solutions.

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Anatomical variants during axillary dissection

Sir
We enjoyed the informative article by Kutiyanawala *et al.* (*Br J Surg* 1998; **85**: 393–4) discussing the anatomical variants within the axilla. They describe six instances of an abnormal band of muscle and/or tendon stretching across the axilla and we feel that this issue needs clarification.

The most common anatomical muscular variant is the 'axillary arch of Langer' (Langer'ser Achselbogen), first described in 1846 and also called the 'axillopectoral muscle'[1]. It arises from the anterior axillary portion of the *latissimus dorsi*, runs across the neurovascular bundle and is inserted into the posterior aspect of the trilaminar tendon of the pectoralis major close to the humerus. Its innervation is via branches of the nerve to pectoralis minor. The muscle is rendered taut by elevation and abduction of the arm and is said to be present in 0·25–7 per cent of the population[2]. In our experience the incidence is 0·8 per cent (17 patients in approximately 2000 axillary dissections).

There have been descriptions of other muscular and tendinous arches in the axilla. They may arise from the *latissimus dorsi*, pectoralis major, thoracic fascia, external oblique aponeurosis or ribs and costal cartilages. We have previously encountered a muscle arising as separate bellies from the lateral aspect of *latissimus dorsi* and serratus anterior, before joining to insert into the humerus[3]. Their insertions are commonly into the trilaminar pectoral tendon, upper humerus or coracoid process. Occasionally, they may insert into the fascia of the arm, extend into flexor muscles of the arm or extend down as the 'chondroepitrochlearis muscle' as far as the medial epicondyle[4]. The innervation of these muscles is frequently from the medial pectoral nerve, thus indicating the embryological origin from the pectoral muscle mass[2]. Others may be supplied by the intercostobrachial, the medial cutaneous nerves of the arm, or the thoracodorsal nerve. They may also be found in association with other muscular abnormalities of the pectoral girdle, for example, the rectus sternalis muscle. It is suggested that these muscular arches of the axilla may be rudimentary phylogenetic remnants of the panniculus carnosus which is well developed in some lower mammalian species, particularly cats[5].

As Kutiyanawala *et al.* have stated the thoracodorsal neurovascular bundle is important for breast reconstruction using the *latissimus dorsi* myocutaneous flap, and if the arch is not divided it may result in an entrapment syndrome and flap ischaemia.

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British Journal of Surgery 1998, **85**, 877–878

Book reviews

Vascular Surgery. A Comprehensive Review. 5th ed.

W. S. Moore (ed.). 285 × 219 mm. Pp. 903. Illustrated. 1998. Philadelphia: Pennsylvania: WB Saunders. Price not supplied.

Some of the most distinguished American vascular surgeons have contributed to this book and important chapters on endovascular techniques have been added. In the preface of the first edition the authors stated that 'the intention of this textbook is to provide a comprehensive review of vascular surgery together with medical and basic science disciplines'. There can be no doubt that the authors have succeeded and, in my opinion, the present book is one of the most important reference works in vascular surgery. The book starts with an interesting historical review followed by valuable chapters on embryology, anatomy, physiology and pharmacology of the arterial wall. There is an excellent chapter on surgical exposures giving detailed and concise information. Haemostasis and thrombosis are well covered and information is given about drug interaction and screening in patients suspected of having coagulopathy. The chapters on atherosclerosis, including haemodynamic factors, are of excellent quality and the same can be said about the description of non-atherosclerotic vascular disease. Good practical advice is given about the treatment of diabetic patients before and after surgery. It is, however, stated that measurement of ankle blood pressure is useful in diabetics. This is in contrast to the general view of preferring toe pressure measurements in this particular group of patients. The chapters on haemodynamics and the vascular laboratory, including information about duplex scanning, are excellent. The technique of measurement of arterial blood pressure of the toe as well as direct measurement of venous pressure might have been included in this chapter. Angiography and interventional radiology are well presented but intentional subintimal angioplasty is not described. The various endovascular techniques including aneurysm repair are up to date and endovascular management of traumatic vessel injuries is reviewed. Endovascular treatment of thoracic aortic aneurysms is not included. The theoretical background, contraindications and practical aspects of thromobolytic therapy is well covered in chapter 20. Regarding evaluation of cardiac risk in patients with vascular diseases I would have preferred the technique of dobutamine stress echocardiography to be included.

Atherosclerotic thoracoabdominal aneurysms are mentioned together with aortic dissections. Perhaps a separate chapter on dissection would have been advantageous as many of these patients are taken care of by vascular surgeons. All aspects of abdominal aortic aneurysm are well presented but more illustrations in this chapter would have made it easier to read. Balloon angioplasty and stenting are not given much attention in the chapter on aortoiliac occlusive disease although this may now be the first option when treating these patients. Infrainguinal occlusive disease is covered fully and sound advice regarding both conservative measures and operative treatment is given. The chapters also include tables of operative results giving the reader the opportunity to compare with his/her own results. Percutaneous transluminal renal angioplasty (PTRA) and stenting are not given much attention in the chapter on renovascular hypertension, probably because stents are not yet approved for this use in the USA. In most European centres PTRA is now the first option in patients with renal artery stenosis whereas open revascularization is used when specially indicated.

Extracranial cerebrovascular disease is extremely well presented by the editor perhaps reflecting his special interest in this field. Supra-aortic vessel disease is included although balloon angioplasty is not given much attention. The chapter covering haemodialysis is excellent and new endovascular approaches are discussed. Complications that might follow arterial surgery are described thoroughly. However, the possibility of using obturator bypass for problems with localized graft infection in the groin is not mentioned. Venous problems including thromboembolic disease and varicose veins are presented in a clear and concise way. In this chapter, a couple of schematic illustrations of the haemodynamics of venous insufficiency and how to separate deep from superficial venous insufficiency would have been useful. Although much attention is given to the problem of selecting the level of amputation, one is left with the impression that the problem has not yet been solved. In general, I would have changed some of the illustrations from operative situations with schematic illustrations or perhaps supplemented them, examples are 36-1c and 36-2c.

Regardless of these insignificant objections, one is left with the impression that this is an excellent review which can be recommended to those with an interest in vascular surgery, including registrar trainees. The references are numerous and of good quality. The review questions are excellent for self-evaluation following each chapter. The quality of the paper is good and most illustrations are of excellent quality. This outstanding book is recommended as one of the reference works that should be available in departments of general and vascular surgery.

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Cybersurgery. Advanced Technologies for Surgical Practice

R. M. Satava (ed.). 155 × 235 mm. Pp. 201. Illustrated. 1998. New York: Wiley-Liss. £55.

This is an intriguing book with a catchy title that is well worth a read. It describes a variety of advanced engineering techniques that are likely to change the nature of surgical procedures as we know them today. Virtual reality, telepresence surgery, computer-aided surgery and microelectromechanical devices are all covered. I was intrigued by the term 'medical avatar' which is a full volumetric representation of the patient that can be used to plan and perform surgery.

In contrast to the futuristic subject the book is irritatingly old-fashioned in format with poor-quality black and white photographs and a few colour plates in the centre. Although the series title is *Protocols in General Surgery* this is essentially a transient book. I read most of it on a train journey and, by coincidence, my daily newspaper had some of the same material in it. It is quite clear that surgical methods are going to change dramatically and this volume offers an insight into the sort of changes we may see surprisingly soon.

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Long-Term Results of Arterial Interventions. European Vascular Course – 1997 Volume

A. Branchereau and M. Jacobs (eds). 278 × 217 mm. Pp. 328. Illustrated. 1997. Armonk: Futura Publishing. US$95.

The book of the *Annual Meeting of the European Vascular Course* is published in English and French, the French originators now inviting English-speaking pundits. Of the 117 contributors, 56 are French and the others generally well-known names in the English literature who are responding to a familiar brief. The exchange of ideas provides insight into Gallic flair for intervention, Anglo-Saxon scepticism, and the mixed tenses and 'franglais' typography provide some amusement. The book has variegated style, modest illustrations and insufficient editorial discipline. Its aims are to disseminate expertise across cultural frontiers. However, while some important results are reported, for example the late complications of aortic grafts, many authors tell us about their large series without stating their criteria for selection or management. A wealth of surgical expertise is thereby squandered in unregulated practice and we finish up none the wiser. We learn that, in more than 3000 carotid procedures, a shunt has been used since 1989 for contralateral occlusion but there are no data to show why (despite 100 references) and we have no guidance on the quality of evidence from some of the acknowledged experts. Carotid bypasses are reported but only patency analysed, and a series of nearly 100 allografts, while stimulating, does not satisfy.

Some chapters undoubtedly have interest and value. Peter Bell gives a clear and well illustrated account with only 18 references, all in English. Some chapters provide an intriguing insight into differences in the clinical situation; for example the Marseilles aortic aneurysm patients, 431 elective but only 26 emergencies. Some authors report experience which does not seem to apply elsewhere. For instance, how is it that in Rouen small vein grafts work better if reversed below the knee? The editors are to be congratulated on their enterprise in promoting the 'entente cordiale' but there is more to do. We have shared our questions and should share the unavoidable responsibility of providing answers. Neither patients nor governments are impressed with mere technique or experience: they want real results.

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This should be not more than 200 words on the second page of the manuscript and be presented in a structured format. **Background:** state why the study was done, and its main aim; **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study: randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings of the study; include important numerical values. **Conclusion:** state the main conclusion drawn from the results. Controversial or unexpected observations may be highlighted, but keep this section brief. Write the abstract in clear prose.

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Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. Do not use the '±' symbol; these statistics should be presented in parentheses after the mean value.

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Clearly describe which methods were used for which analyses; any methods not in common usage should be supported by references. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value, e.g. '$t = 1 \cdot 34$, 16 d.f., $P = 0 \cdot 20$'.

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Interpretation

Do not confuse statistical significance with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data.

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Type the references with double spacing in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged. Reference to unpublished communications will not be accepted. Cite personal communications in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

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Eurosurgery 98

This supplement contains the abstracts of papers to be presented during the Eurosurgery 98 Meeting in Budapest. The quality of the material to be presented is self-evident from these pages. The abstract selection has been, as usual, rigorous and thorough. The *British Journal of Surgery* is pleased to produce this abstract book as a supplement, as a sign of our continuing association with Eurosurgery.

The Journal wishes every success to the meeting of Eurosurgery 98. The Editors of this supplement hope that all participants have an enjoyable and stimulating meeting.

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Stomach

Adjuvant chemotherapy using fluoro-uracil, epirubicine and cisplatine (FEP) after curative resection of gastric carcinoma

J.L. Bouillot, K. Aouad, D. Heudes, C. Boiron, F. Aimé, S. Oudard, L. Chauvenet, E. Pujade Lauraine, J. Fourmestraux, J.H. Alexandre and J.P. Béthoux *Departments of Surgery and Biostatistics, Hôpitaux Broussais et Hôtel Dieu, 1, Place du Parvis Notre Dame, 75004 Paris, France*

Aim: The benefit of adjuvant chemotherapy (AC) after curative resection for gastric carcinoma is still debated. This prospective phase II trial analysed our experience with adjuvant chemotherapy after gastric resection for adenocarcinoma.
Patients and methods: Eighty-seven patients with gastric adenocarcinoma underwent gastrectomy as primary surgical management between January 1990 and December 1995 (52 males and 35 females, mean age: 64·3±13·2 years). There were 20 palliative resections and 67 curative ones (37 distal gastrectomy and 50 total gastrectomy). A chemotherapy of FEP (four courses of fluoro-uracil, epirubicin, cysplatin) was postoperatively proposed after curative resection for 25 patients <75 years, in good status (OMS <2) with a histopathological examination showing nodal invasion.
Results: The types of gastrectomy performed were 18 D 1, 41 D 2, 8 D 3, with the mean number of lymph nodes removed 13·8. The staging of tumours, according to the pTNM classification, in the AC group was stage I: two patients; stage II: two patients; stage III: 19 patients; stage IV: two patients vs 14 patients stage I, 11 patients stage II, 16 patients stage III, one patient stage IV in the non-AC group. Chemotherapy was globally well tolerated. It had to be stopped in one case, the dose reduced in three cases, and was accompanied with digestive troubles in six cases. The median survival for the 67 patients with curative resection was 38 months (ED 14·7). It was 38·1 months (ED 12·8) in the subgroup AC vs 51·6 months (ED 23·9) in the absence of AC ($P<0·0001$). This better prognosis concerning the group without AC was due to the large number of patients (19/42) without nodal invasion. In the subgroup of stage III patients, the median survival was 38·1 months (ED 10·5) with AC vs 17·5 months (ED 11·7) without AC ($P=0·19$).
Conclusion: Adjuvant chemotherapy of FEP type seemed to improve survival after curative gastric carcinoma resection, especially for stage III patients with nodal invasion. Its benefits need to be evaluated in large prospective randomized trials.

Prognostic value of p53 protein in colorectal carcinoma

M. Diez, A. Gutiérrez, A. López, P. Martínez, P. Hernandez, A. Martín, J.M. Mugüerza, R. Villeta, A. Ruiz, F. Noguerales and J. Granell *Cirugía General, Hospital Universitario Príncipe de Asturias, 28805 Madrid, Spain*

Aim: To analyse the prognostic value of a set of pathological variables after curative resections for large bowel adenocarcinoma and to test a prognostic score derived from factors with independent predictive effect.
Material and methods: The study is based on data from 292 consecutive unselected patients (B–C Astler–Coller stages). Histopathological features were evaluated prospectively on resected primary tumours. Relationship between factors and risk of recurrence was assessed by a Cox's proportional regression analysis.
Results: Four variables retained independent prognostic significance with respect to the risk of tumour recurrence: extent of bowel wall invasion (intramural vs extramural), peritumoral lymphocytic infiltration (present vs absent), number of positive nodes (none vs one to four vs more than four) vascular invasion (present vs absent). A prognostic score was defined with those four variables. Each variable was weighted according to the regression coefficient attained. This system revealed four prognostic groups. Group I (scores 0·5–1) included 42 (14 per cent) patients, Group II (scores 1·5–2) included 103 (35 per cent), Group III (scores 2·5–3) 127 (43 per cent), and Group IV (scores 3·5–4) 20 (7 per cent). Tumour recurrence was detected in two (5 per cent) patients of Group I, 16 (15 per cent) in Group II, 44 (35 per cent) in Group III, and 13 (65 per cent) in Group IV ($P<0·001$). Five-year disease-free survival was 95 per cent in Group I, 60 per cent in II; 46 per cent in III; and 24·4 per cent in IV ($P<0·01$).
Conclusion: A prognostic score based in the evaluation of four histopathological parameters concerning the tumour phenotype, enables the identification of subgroups of patients with different risk of relapse after curative resection of colorectal adenocarcinoma.

Prognosis of surgical treatment of gastric cancer according to extend lymphadenectomy

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Aim: The worldwide decrease in the incidence of gastric cancer over the last 10 years has not been observed in our environment where it remains as an important social problem due to its high morbidity and mortality. We proposed to evaluate if extended lymphadenectomy produces better results.
Material and methods: Between 1987 and 1991, 193 gastric cancers were diagnosed. A total of 162 (84 per cent) were reviewed 5 years after surgery. Out of them, 121 (63 per cent) could be resected, 59 with a R1 and 62 with a R2 lymphadenectomy. Characteristics of this group of 121 patients are analysed regarding age, gender, size and tumour location, histological type and surgical procedures according to tumour stage.
Results: They were analysed five years after surgery. Perioperative mortality was five cases (8·4 per cent) in the R1 group and four (6·4 per cent) in the R2 group. Morbidity was similar in both groups. Cardiopulmonary complications occurred in two (3·38 per cent) of the R1 group, and three (4·83 per cent) of the R2 group. Urinary infection occurred in five (8·47 per cent) of the R1 group and four (6·45 per cent) of the R2 group. Intra-abdominal abscesses occurred three times (5·08 per cent) in the R1 group and twice (3·22 per cent) in R2. R2 resection showed a higher incidence of suture dehiscence (six cases (9·67 per cent) vs four (6·77 per cent) in R1 group). On the other hand R1 group showed a higher incidence of surgical wound infection nine (15·25 per cent) vs seven (11·29 per cent) in R2. Recurrence occurred in 45 patients in the R1 group and 41 in the R2 group. 5-year survival was nine patients (15·2 per cent) in the R1 group and 17 (27·41 per cent) in the R2 group.
Conclusions: Best results were achieved in distal located lesion. R2 lymphadenectomy seems to improve prognosis in stages II and III. Extended total gastrectomy showed a survival rate of 37 per cent, subtotal extended 24 per cent and subtotal resection 23·6 per cent.

Percutaneous endoluminal grafting for femoro-popliteal disease: a feasibility study

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Aims: A feasibility study was carried out to assess the role of a balloon mounted ePTFE graft with proximal and distal anchoring stents in patients with disabling claudication considered unsuitable for angioplasty because of the severity of the disease.

Methods: Thirty-one patients with claudication were considered suitable for treatment. All had significant disease confined to the superficial femoral artery (SFA) and satisfied the entry criteria of two or more vessel run off and minimum SFA diameter of 4 mm at stent anchor sites. Procedures were performed under local (17), epidural (2) or general (12) anaesthesia, using a 9F introducer sheath, intravascular ultrasound (IVUS) and an image intensifier.

Results: Successful deployment of the stent grafts was achieved in 23 cases, with eight failures. Five were excluded following IVUS interrogation, two after encountering difficulties with the introducer sheath and one-following device failure. Of those patients in whom graft deployment was successful primary patency was achieved in 10 (43 per cent) and secondary patency in 14 (60 per cent) at 1 year follow-up.

Conclusions: While initial results with this device have proved disappointing, current development in the design of this stent graft to one which is fully supported may result in this becoming a viable alternative to angioplasty or indeed surgery.

REDO surgery for the treatment of late complications in a 10-year follow-up of 441 reconstructive operations

Á. Balogh, R. Sipka and R. Ménesi *Albert Szent-Györgyi Medical University Department of Surgery, P.O. Box 464, H-6701 Szeged, Hungary*

The purpose of this study is to review 120 REDO operations performed at the surgical clinic of the Szentgyörgyi Medical University Szeged. These operative corrections (or late reoperations) were performed to treat late complications – reocclusion, anastomotic aneurysm, graft infection – of 441 aorto-iliac reconstructions, and were performed in a 5-year period (1986–1991). The REDO operations were done from three months to 10 years after the first interventions. Twenty-five REDO procedures (21 per cent) were performed to correct an anastomotic aneurysm, and 95 (79 per cent) to treat the reocclusion of the former reconstructed vessels. The REDO interventions proved to be necessary with a 10 per cent higher frequency after thrombendarterectomies than after bypass procedures. Following resections of the abdominal aorta due to aneurysms a REDO intervention was done in a 5 per cent lower ratio than after reconstructions to treat arteriosclerotic obliterations. The author evaluates the surgical technique of REDO surgery, gives an overview of the possibilities for surgical correction, and analyses the results of the 120 interventions.

Can clinical evaluation and noninvasive testing substitute for angiography in the evaluation of carotid artery disease?

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Aim: The objective of this study was to prospectively assess the value of combining clinical evaluation and non-invasive testing, particularly Duplex scanning, in determining the safety and accuracy of performing carotid endarterectomy (CEA) without angiography.

Methods: During the last 9-month period, 17 patients underwent 14 CEAs without angiography. This was a prospective but non-randomized study, since precise selection of those patients subjected to CEA without angiography was practised. The indications for proceeding with CEA without angiography were as follows: 1) the progression of the carotid lesion with contralateral internal carotid artery (ICA) previously operated on with angiography; 2) renal insufficiency; 3) the need for emergency operation; 4) the need for concurrent operation in another anatomic region; 5) surgeon's preference. The patients ranged in age from 56 to 81 years, with a mean age of 72 years. All patients were preoperatively evaluated by the same neurologist and studied by duplex scanning and CT scan. Thirteen patients were symptomatic: no symptomatic patient presented with non-hemispheric symptoms. In all cases the ICA lumen reduction was ≥70 per cent. All operations were performed under general aesthesia with continuous EEG monitoring for the selective use of an intraluminal shunt (IS). All procedures were carotid eversion endarterectomy and reimplantation of the ICA in the common carotid artery. The data from ultrasound imaging were correlated with surgical findings and pathological specimens.

Results: Perioperative stroke risk and mortality rates were 0 per cent. The predicted carotid lesion was confirmed by the operative finding, at the time of exploration, with respect to high grade stenosis and the characteristics of the pathologic specimen in all 17 cases.

Conclusions: The major criticisms of the sole noninvasive evaluation are: 1) the inability to determine intrathoracic pathologic abnormalities of the carotid vessels, and 2) the possible coexistence of incidental, asymptomatic intracranial berry aneurysm or unrecognized intracranial stenotic or occlusive siphon disease. Since these exceptions are rare and may be easily overcome, CEA can be performed safely without angiography, on the basis of clinical assessment and duplex scanning solely, when the accuracy of the vascular laboratory has been carefully and scientifically established.

Duplex vein mapping of proximal deep vein thrombosis: a study of 2034 lower limbs

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Aim: To evaluate the anatomic distribution, extent and patterns of proximal lower limb DVT in a large series of patients with clinically suspected DVT.

Materials and methods: The venous system of 2034 consecutive lower limbs was investigated using colour duplex imaging (ATL Ultramark 9; 5 MHz transducer). Criteria for a positive scan were: intraluminal echogenic material, non-compressibility, blood flow around a lucent filling defect, absence of intraluminal Doppler signal, continuous signal not phasic with respiration, reduced or absent flow with distal augmentation and image irregularities despite optimal settings.

Results: Supra-inguinal thrombosis was identified in 50 (2·45 per cent) limbs. Thrombosis in the common femoral vein (CFV) was detected in a total of 143 limbs (7·03 per cent). It was associated with a supra-inguinal clot in 47 limbs (32·8 per cent) and thrombosis of the superficial femoral vein (SFV) in 107 limbs (74·8 per cent), the popliteal vein (PopV) in 76 (53 per cent), the tibio-peroneal trunk (TPT) in 15 (10·5 per cent) the posterior tibial vein (PVT) in 28 (20 per cent), the peroneal vein (PerV) in 29, the soleal vein (SolV) in 17 (12 per cent) and the gastrocnemial veins (GasV) in 13 (9 per cent). Of these limbs, 41 (28·6 per cent) had sustained a previous DVT.

Thrombosis in the SFV was detected in a total of 226 limbs (11·1 per cent). It was associated with CFV and supra-inguinal thrombosis in 107 (47 per cent) and 39 limbs (17 per cent) respectively. DVT in SFV was associated with thrombosis in the PopV in 153 limbs (67·7 per cent), the TPT in 34 (15 per cent), the PTV in 60 (26·5 per cent), the PerV in 62 (27·4 per cent), the GasV in 26 (11·5 per cent) and the SolV in 31 (13·7 per cent). Of these limbs, 51 (22·5 per cent) had sustained a previous DVT.

Popliteal vein thrombosis was detected in 211 (10·3 per cent) legs and was associated with proximal DVT in 153 (72·5 per cent) of which 33 (15·6 per cent) suprainguinally; distal thrombosis involved the TPT in 46 (21·8 per cent), the PTV in 74 (35 per cent), the PerV in 75 (35·5 per cent), the anterior tibial vein (ATV) in 32 (15·1 per cent), the GasV in 37 (17·5 per cent) and the SolV in 46 (21·8 per cent).

The PTV, PerV and SolV were the most frequently thrombosed calf veins. PTV and PerV thrombosis with or without the SolV was the pattern of calf DVT most often seen. GasV thrombosis was present only in 1/3 of soleal DVT.

Only 16 per cent of limbs with suspected DVT had proximal thrombosis.

Conclusions: Thrombosis in the CFV, SFV and PopV is associated with more proximal disease in 32·8, 47 and 72·5 per cent, respectively. The more distal the thrombus the higher the likelihood of a more proximal one detected. The SFV is the most frequently thrombosed proximal vein with 22·5 per cent of affected limbs having sustained a previous thrombosis. The most frequently seen pattern of proximal thrombosis involves both the SFV and PopV with or without the PerV and PTV. Involvement of the PTV and PerV with or without the SolV is the most frequently seen pattern of multifocal calf DVT.

Treatment of arterial graft infection by in situ replacement with allogenic arterial graft

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The present standard therapy of aortic graft infection is connected with frequent occurrence of operative and late complications. Autogenous tissue revascularization techniques are very promising therapeutic alternatives, but their usefulness is limited by the complexity of this procedure and by the lack of suitable donor vessels. In recent years a few reports have described the possibility of replacing an infected vascular graft with an allogenic arterial graft.

From January 1996 until November 1997 nine patients with aortofemoral graft infection were treated in our department. Because of the extent of infection it was impossible to perform extra-anatomic graft. In all cases infected vascular grafts were removed and in situ arterial allograft were inserted. The allografts were taken from multiorgan donors and cryopreserved in liquid nitrogen in 20 per cent dimethylsulfoxide (DMSO).

There were no intraoperative deaths observed. One critically ill patient with severe Pseudomonas sepsis and extensive retroperitoneal abscess died on the second postoperative day, due to septic shock. One patient died in the 20th postoperative day due to myocardial infarction. In all seven survivors infection could be eradicated and during the follow-up period they remained well.

The arterial allografts seem to be the alternative in prostheses infection treatment.

High resolution ultrasound prior to endarterectomy: the accuracy of grading ICA stenosis

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Aim: The aim of this study was to evaluate the accuracy of ultrasonic B-mode images of ICA in estimating the degree of stenosis.

Material and methods: In a random consecutive series of patients scheduled for CEA routine duplex scanning was performed using ATL HDI 3000 and 7–4 MHz probe. Good quality images in B-mode (both in longitudinal and transverse views) were frozen on the screen. The percentage diameter and area reduction were calculated from each view respectively. Peak systolic (PSV) and end diastolic velocities (EDV) were measured at the proximal CCA and ICA within the jet of turbulence. The following velocity ratios were used to calculate the degree of haemodynamic stenosis (PSVic/PSVcc), (EDVic/EDVcc) and (PSVic/EDVcc). Endarterectomy specimens of the same patients were scanned immediately in a mixture of saline and gel media. The site of maximal stenosis was marked and 0·2 mm transverse pathological blocks were obtained. The duplex measurements were compared to the percentage area and diameter reduction from transverse sections of the specimens. A millimetre scale was placed next to the specimens which was captured by video. The area reduction was measured by playing the video and using the same duplex setting as above.

Results: The following table summarizes the difference in the estimated diameter stenosis using different methods in relation to that estimated from endarterectomy transverse blocks (as a gold standard). Twenty-nine out of 32 were in the region of 70–99 per cent.

Duplex method used	Percentage of cases with concordant stenosis to that estimated from the surgical specimens	Percentage of cases with disconcordant stenosis relative to that estimated from the surgical specimens
B-mode images	93%	6%
PSVica	79%	21%
EDVica	24%	76%
PSVica/PSVcca	76%	24%
EDVica/EDVcca	60%	40%
PSVica/EDVcca	76%	24%

Conclusion: The results indicate that images obtained with B-mode are the most accurate in determining the degree of stenosis. Diameter and area reduction (measured on duplex) might be more appropriate parameters to be used in studies that evaluate the sensitivity and specificity of ultrasound with angiography as gold standard.

Acute normovolaemic haemodilution in repair of abdominal aortic aneurysm: autolologous transfusion and cost reduction

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Aim: To review the practice of acute normovolaemic haemodilution (ANH) in routine abdominal aortic aneurysm (AAA) repair in a single vascular unit with analysis of financial implications.

Patients and methods: Retrospective analysis of case notes, operation records and anaesthetic charts was undertaken for 80 randomly selected patients who had undergone routine AAA repair (1990–1997). Demographic and operative details were noted along with blood cross-matching, blood loss and per and postoperative transfusion practice. Pre and postoperative haemoglobin (Hb) concentration and packed cell volume (PCV) were recorded. Outcome of surgery was assessed by observing 30-day mortality, postoperative morbidity and length of hospital stay. Economic analysis was used to estimate potential cost savings.

Results: Of 80 patients studied 72 (90 per cent) had complete records suitable for analysis. Thirty-two patients had ANH preoperatively (group 1), 40 did not (group 2). Mean (range) volume of ANH blood for autologous transfusion was 700 (400–1200) ml. Of all the parameters measured only the number of units of blood cross matched preoperatively (median values: four units group 1 vs six units group 2) (Mann–Whitney, P=0·0035) and the number of units transfused peroperatively (median values: 0·5 units group 1 vs two units group 2) (Mann–Whitney, P=0·0065) were significantly different. Comparing the cost of equipment used for ANH and the cost of cross matching heterologous blood there is a saving of £70 per operation if ANH is used.

Conclusion: The results suggest that ANH is a safe procedure prior to routine AAA repair and has definite economic advantages over heterologous transfusion. The theoretical decreased risk of infection and transfusion reaction as well as increased oxygen carrying capacity of autologous blood warrant further research.

The prevalence of Factor V (G1691A) and methylenetetrahydrofolate reductase (C677T) gene mutations in Turkish patients with arterial thrombosis

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Although Factor V G1691A (FV) mutation is a well recognized genetic risk factor for venous thrombosis, its role in patients with arterial thrombosis needs to be clarified. As the individuals carrying this mutation may be asymptomatic, there might be a possible interaction with other risk factors such as point mutation at C677T in the 5'-10'-methylenetetrahydrofolate reductase (MTHFR) gene. FV and MTHFR are frequent in the general population and coinheritance may further increase the risk of thrombosis. Therefore, we investigated the prevalance rate of FV and MTHFR gene mutations in patients with arterial thrombosis and healthy controls. All subjects and controls were from Central Anatolia. Fifteen (3F) patients with the median (range) age of 59 (20–77) years and 90 (50F) with the median (range) age of 31 (20–73) years were studied. DNA was extracted using conventional methods followed by PCR amplication and restriction endonuclease digestion. Digested PCR products were identified using agarose gel and stained with ethidium bromide.

Of the 15 patients with arterial thrombosis four (27 per cent) had heterozygote FV gene mutation whereas eight (53 per cent) had heterozygote MTFR and one had homozygote MTHFR gene mutation. Out of 90 healthy controls, seven (8 per cent) had FV gene mutation whereas 29 (32 per cent) had heterozygote MTFR and six (7 per cent) had homozygote MTHFR gene mutations. Coinheritance of heterozygote FV and MTHFR was found in 75 per cent of patients with arterial thrombosis which was 43 per cent in healthy controls.

The increased rate of prevalence and coexistence of both FV and MTHFR found in this group of patients suggesting that these mutations might increase the risk of arterial thrombosis but it needs further investigation.

In situ repair or extra-anatomic reconstruction for treatment of aorto-enteric fistulas

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Based on 23 own observations and 208 patients with aorto-enteric fistulas (AEF) collected from the literature, actual diagnostic methods and its surgical approach are discussed.

The most frequent location both of primary and secondary aorto-enteric fistulas is the endpart of the duodemum. In the group of secondary AEF the paraprosthetic type represents the most frequent morphological finding. The choice of surgical repair is still controversial. Numerous surgeons however insist on a radical repair (Type A: restoration of the intestinal tract, complete removal of the vascular prosthesis, blind closure of the infrarenal aortic stump and axillo-bifemoral bypass. As an alternative surgical approach an in situ repair is presented (Type B: closing of the intestinal defect, partial exchange of the inserted vascular prosthesis, an encircling omentum sleeve covering the prosthesis and anastomoses).

Type A is loaded with a high operative mortality (52 per cent) and frequent secondary complications (e.g. recurrent AEF, bleeding from the aortic stump). The Type B repair offers a time-saving procedure with a reduced operative mortality (22 per cent) and a better outcome for the patients. The only contraindication for this method is the presence of an extensive infection of the retroperitoneal space including the vascular prosthesis.

Patients with low-grade aortic graft infection benefit from partial graft resection and in situ repair.

Long-term results of 716 PTFE grafts for dialysis: analysis of different graft sizes and configurations

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Aim: The purpose of this presentation is to analyse the complication rate of 716 PTFE grafts for dialysis, and calculate their primary and secondary patency rates.

Material and methods: Between 1981 and 1997 2565 vascular accesses were performed: 1259 radiocephalic arteriovenous fistulas (AVF) (67 per cent), 468 upper arm AVF (18 per cent), 82 dacron cuff catheters (3 per cent) and 716 PTFE grafts (28 per cent). Anatomical positions of grafts were as follows: upper-arm (6–8 mm): 324 (45 per cent); upper-arm (6 mm): 184 (26 per cent); straight forearm (6 mm): 96 (13 per cent) curve forearm (6 mm): 49 (7 per cent); brachiojugular (6 and 6–8 mm): 51 (7 per cent); femoro-fermoral (6–8 mm): 12 (2 per cent). Retrospective study. Parametric analysis was done with Student's *t*-test. Graft surviva was calculated using the life-table method.

Results: Overall complication rate was 0·49 episodes per graft-year o follow-up. Complication rate (episodes per graft-year) was significantl lower in 6–8 mm upper arm grafts (0·33) ($P<0{\cdot}001$), compared with th other grafts (6 mm upper-arm = 0·57; 6 mm straight forearm = 0·62 brachiojugular = 0·72; 6 mm curve forearm = 0·74). Overall primar patency was 70 per cent, 34 per cent and 12 per cent at 1, 5 and 10 years Overall secondary patency (after successful rescue surgery for complications) was 86 per cent, 66 per cent and 39 per cent at 1, 5 and 10 years Best patency rates were observed in 6–8 mm upper-arm grafts: primary 92 per cent, 52 per cent, 24 per cent at 1, 5 and 10 years; secondary, 9 per cent, 79 per cent and 54 per cent at 1, 5 and 10 years.

Conclusions: 1: 6–8 mm upper-arm grafts (8 mm grafts tapered to 6 mm at the arterial side) show the lowest complication rate and best long-term survival. 2: Brachiojugular grafts can be an alternative in cases of non dilatable subclavian vein stenosis or occlusion.

Non-operative treatment of false aneurysms using percutaneous injection of fibrin adhesive

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Traumatic false aneurysms often require operative repair if duplex-guided compression fails. We describe a percutaneous technique of occlusio which preserves the artery of origin and avoids the use of metallic coil and endovascular stents.

This technique was attempted in 13 patients with peripheral false arterial aneurysms where duplex-guided compression had failed over an 18 month period. In each case an angioplasty catheter was placed across th neck of the aneurysm and inflated until flow within the sac was occlude Duplex scanning confirmed this and under ultrasound guidance, 3 ml o tissue adhesive (Beriplast – P) was injected percutaneously into the sa during flow occlusion. Once thrombus production was confirmed o duplex with the angioplasty balloon deflated, the needle and angioplast catheter were withdrawn.

Ten femoral, two popliteal and one posterior tibial aneurysms we treated with this technique. Two femoral aneurysms demonstrated min flow on completion, but complete occlusion on repeat duplex at 24 hour One patient developed a small false aneurysm at the site of insertion o the angioplasty catheter which closed spontaneously. One patient died day 2 (cause unrelated to this technique). In all cases the false aneurys was successfully occluded with preservation of the artery of origin.

This technique potentially avoids operative repair of false arteri aneurysms in patients where duplex guided compression has failed and associated with minimal complications.

Colonoscopy with biopsy after aortic surgery: a unique study of the incidence of colonic ischaemia

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Aims: Colonic ischaemia is a well documented complication of abdominal aortic reconstruction. This is the first prospective study in which all patients have had routine pre- and postoperative colonoscopy and biopsy, in order to determine the true incidence and implications.
Methods: Fifty-six patients undergoing elective infrarenal aortic surgery, 28 for aneurysm and 28 for occlusive disease, were colonoscoped and biopsied pre and one week postoperatively.
Results: All patients had normal macroscopic and microscopic appearances on preoperative biopsies. A 30 per cent incidence of postoperative colonic ischaemia was identified by histology (16/53 patients), almost half of these (7/16) having normal macroscopic appearances. Two factors exhibited a statistically significant association with development of ischaemia: prolonged cross-clamp time (mean of 44·75 vs 35 minutes, $P<0·05$, Mann–Whitney U test) and postoperative diarrhoea (88 per cent vs 13 per cent, $P<0·001$, Fisher's exact test). Co-morbidity was much higher in those patients with ischaemia (81 per cent vs 13 per cent, $P<0·005$, Fisher's exact test). Overall morbidity was significantly greater in the aneurysm group (46 per cent vs 21 per cent, $P<0·05$, Fisher's exact test).
Conclusion: Colonic ischaemia after aortic reconstruction is a much more common occurrence than previously reported, and though mild and transient in many cases, is still associated with significant morbidity. When suspected, colonoscopy with biopsy is recommended.

Oesophageal epidermoid carcinoma: results of surgery after neoadjuvant radiochemotherapy

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While surgery still remains the treatment of choice for oesophageal epidermoid carcinoma, there was no improvement of the survival rate in the past decades with 18 per cent 5-year actuarial survival. The aim of this study was to evaluate the interest of surgery after neoadjuvant radiochemotheraphy to 1) increase the resection rate; 2) improve the actuarial survival rate; 3) increase the disease-free survival (DFS); 4) avoid mutilating surgery. From February 1987 to September 1997, 55 patients (49 men and six women) with a mean age of 58·8 years (from 38 to 77) received oesophageal resection after neoadjuvant treatment. In eight cases there was a previous history of ENT epidermoid carcinoma. Tumour location was: upper 1/3 *n*=19, middle 1/3 *n*=22, lower 1/3 *n*=9 and double localization in upper and lower 1/3 *n*=5. Impassable stenosis was observed in 20 cases. Thirty-five patients had endosonography, and tumour classification was mainly uT3 *n*=25 (45·5 per cent), uT4 *n*=6 (11 per cent) and uN1 *n*=25 (45·5 per cent), uN2 *n*=6 (11 per cent), the other patients were: uT0 *n*=1, uT1 *n*=1, uT2 *n*=4, uTx *n*=3, uN0 *n*=5, uNx *n*=4. Neoadjuvant treatment included two courses of chemotherapy 5-FluoroUracil (1 g/m^2/day) and Cisplatyl (25 mg/m^2/day) from day 1 to day 5, and from day 21 to day 26 where half dose of 5FU was given. Radiotheraphy was done from day 21 to day 36 giving a total of 36 grays. Full neoadjuvant treatment was possible in 67·3 per cent of cases, radiotherapy was completed in 85·5 per cent, and uneventful course was achieved in 56·4 per cent. Surgery was performed one month after the end of radiotherapy (at day 60). Tumour resectability was 96·4 per cent, only two patients had surgical exploration without tumour resection. Complete (curative) resection was achieved in 45 cases (82 per cent), and in eight cases (14·5 per cent) palliative resection was done. Forty-seven patients had gastroplasty and two had coloplasty. Three field lymphadenectomy was done in 38 cases (69 per cent) and two field lymphadenectomy in 15 cases (27 per cent). Operative mortality was nil, and hospital mortality was 7·3 per cent. The postoperative course was uneventful in 45·5 per cent of patients, complications that occurred were mainly pulmonary (34·5 per cent) and recurrent nerve palsy (23·6 per cent). Pathological tumour classification (AJCC 1988) was: Stage 2a *n*=6, Stage 2b *n*=3, Stage 3 *n*=8 (14·5 per cent), Stage 4 *n*=13 (24 per cent), and in 23 cases (42 per cent) the tumour was totally (or almost) sterilized (R±). Larynx preservation was achieved in 10 of 12 patients with theorectical indication of total pharyngolaryngo-oesophagectomy. The overall actuarial survival rate was 27 per cent and 22 per cent at 4 and 9 years. The DFS was 28 per cent and 25 per cent respectively Sixteen patients died with local or metastastic recurrence, and 19 are living (17 are disease free and two with metastasis). In the group R±, the actuarial survival rate was 53 per cent and 46 per cent at 4 and 9 years, and the DFS was 46 per cent and 47 per cent respectively. Six patients died without recurrence and 12 are living and disease free. Neoadjuvant treatment is well tolerated by almost all patients when carefully selected. It appears that this combination therapy increases tumour resectability, it can allow in some cases laryngeal preservation. Significant improvement of the actuarial survival rate and DFS is observed in the R± group.

Barrett's oesophagus: indications for resection

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The aim of this retrospective study was to assess the indications and the results of oesophageal resection for Barrett's oesophagus (BO).

From 1992 to 1997, 20 patients with histologically proven BO underwent resection: 19 males, 1 female, mean age 66. During the same period, 145 oesophagectomies were performed for other reasons, and five patie with a BO underwent an antireflux procedure. Oesophagectomy was p formed via abdominal and right thoracic approach in nine cases, with thoracotomy in seven cases and via a left thoracic approach in four cas

Postoperative pathology showed 19 adenocarcinomas and one h grade dysplasia (HGD). Five patients had previous diagnosis of BO, whom three were under an endoscopic surveillance programme. T pathology of these three patients showed one HGD and two T_1 tumou while in the two others, tumour was classified T_3 N_1.

There were two postoperative deaths (10 per cent) from pulmon complications. The 3-year actuarial survival rate was 48 per cent.

In conclusion, resection is rarely indicated for BO, and mainly invasive carcinoma. Long term results can be improved if oesophag tomy is indicated for HGD or early stage carcinoma, condition possi diagnosed by an endoscopic surveillance programme of BO.

Laparoscopic approach for redo antireflux surgery

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Background: In general, reoperations after failed antireflux surgery performed as an open transthoracic or abdominal procedure and lapa scopic refundoplication is still controversial.
Aim: To analyse the surgical and functional results following lapa scopic redo antireflux surgery.
Methods: Fourteen patients (nine male, five female; age: 13–52 yea have been scheduled for laparoscopic refundoplication since 12/93. these, 11 had previous antireflux operations performed in other hospit Three of the 110 patients (2·7 per cent), who had antireflux surgery in clinic, needed a second operation. The indication for surgery was rec rent reflux in 10 and severe dysphagia in four patients. Patients were c sidered for a laparoscopic approach, if they had previous laparosco antireflux surgery (*n*=5), only attempt for an open fundoplication (*n*= or one or more open operations with gastropexia (*n*=5). Follow-up exa inations were done after 1–4 years (median: 19 months).
Results: A laparoscopic refundoplication was completed in eight of 14 patients (57 per cent). Because of severe adhesions conversion w necessary in three patients following fundoplication and in three patie following gastropexia. Outcome at follow-up examination was rated go or excellent in all patients. No one complained of dysphagia and regur tation. Mild heartburn was present in two patients, and occasional g bloat in four patients.
Conclusion: Laparoscopic refundoplication is useful especially patients following laparoscopic fundoplication. The results are similar those with the first antireflux procedure. Refundoplication in a patient f lowing an open procedure frequently requires an open procedure.

Long term clinical evaluation of oesophageal reconstruction

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Introduction: During a 25 year period (between 1964 and 1990) 7 patients underwent oesophageal reconstruction. The most common reco structive operations were: long segment isoperistaltic colon substituti after corrosive ingestion not responding to other methods of treatme distal esophageal interposition of the jejunum and gastric tuba (cervic EGA). To assess long-term results of various methods of reconstructi we randomized 150 patients (22 per cent) for control study. Only cooperative patients arrived to the clinic for an interview and the contr examination. There were 10 patients operated for carcinoma and patients with benign lesions operated in the period of 5 to 25 years ago

Methods: All operated patients were divided in five groups: right colon oesophagoplasty (17 patients), left colon oesophagoplasty (20), gastric tube (10), interposition of the jejunum (10) and Roux-en-Y reconstruction (five patients). Ten healthy volunteers were examined in the same time as a control group. The clinical evaluation has been achieved by a personal interview (side effects, ability to swallow and eating habits), clinical examination (body weight, barium swallow and endoscopy) and functional tests (radionuclide scintigraphy – transit time and clearance). All examined patients were classified in three groups – excellent, good and poor. In categorizing the patients according to our results, excellent and good patients were selected who had no symptoms related to feeding, clinical evaluation and functional tests were negative. The outcome was considered good to poor if the patients occasionally experienced temporary symptoms, medium clinical results and tests and poor with severe symptions, clinical results and test which cause an incapacitation and need for another corrective operation.
Results: In overall long-term (5–21 years) control examination of 62 patients, 69·35 per cent had an excellent to good results, 25·80 per cent had a good to poor results and only 4·8 per cent had poor results. The best long term results (8–10 years after surgery) we found in the group of patients with short jejunal interposition. All these patients showed almost normal behaviour and normal clinical and functional tests. On the second place is long isoperistaltic left colon substitution (5–21 years). After this type of reconstruction the patients must modify their eating habits but had no swallowing difficulties. Regurgitation and gastrocolic reflux with colitis were not common but we found colonic stasis in almost 50 per cent of patients. Only 5 per cent of patients had persistent weight loss. In most of the patients propulsive activity of the colon was difficult to quantify. In the group of patients with right colon reconstruction the long term results were a little better in the left colon. On the third place we found long term results after gastric tube reconstruction (5–10 years). Reflux esophagitis is dependent of the level of EGA but we found it in 20 per cent in high anastomosis.
Conclusion: In comparing our results with other series bypass reconstruction has some advantage because of vagotomy after oesophagectomy and also postoperative mortality is higher than in bypass reconstruction.

Has the expansion of laparoscopy modified the medical habits in the treatment of the gastro-oesophageal reflux

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Between 1992 and 1996, 42 patients had a Nissen fundoplication for gastro-oesophageal reflux. There were 29 men and 13 women, the median age was 37 years (range: 25–65). One patient was lost to follow-up. The other patients were evaluated in December 1997, the median follow-up was 30 months (range: 12–72). We recorded one bad, four good and 36 excellent results. We distinguished between two groups to determine whether the expansion of laparoscopy had modified or not the management of the patients presenting with peptic oesophagitis. Group A consisted of 15 patients operated on between 1992 and 1994 and group B of 27 patients operated on between 1995 and 1996. A minority of patients (5/15=33 per cent) were treated by laparoscopy in group A and a majority (22/27=81 per cent) in group B ($P<0\cdot005$). The Nissen fundoplication represented 1·2 per cent (15/1216) of the global surgical activity in group A and 2·9 per cent (27/925) in group B ($P<0\cdot01$). The postoperative results were equivalent in the two groups. Patients of group A had complained of gastro-oesophageal reflux for 7±5 years and patients of group B for 5±3 years (NS) before being referred for surgery. The number of gastroscopies and the length of the medical treatment before surgery were also equivalent in the two groups: respectively 7±2 gastroscopies and 32±15 months in group A vs 6±3 gastroscopies and 26±12 months in group B (NS). It has to be noted that several patients were referred to the surgeon by a friend or by the general practitioner while they had never been informed by the gastroenterologist about the potential benefit of a surgical operation. That situation occurred in three patients (20 per cent) of group A and in eight patients (29 per cent) of group B (NS). In our experience, Nissen fundoplication is a successful procedure in 97 per cent of the patients. With the expansion of laparoscopy, we have noted that the patients are not referred quickly to surgery but that the number of operations performed for gastro-oesophageal reflux has increased significantly. Finally, it is clear that some gastroenterologists still have to be convinced of the role of surgery in the treatment of the gastro-oesophageal reflux.

Adenocarcinoma on Barrett's oesophagus: a series of 44 resections

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Introduction: The incidence of lower esophageal adenocarcinoma is increasing. The responsibility of Barrett's oesophagus may be suspected. This study reviews the results of a surgical approach.
Methods: Between 1982 and 1997, 44 adenocarcinomas on Barrett's oesophagus were resected among 120 type I and II adenocarcinomas. The mean age of the 40 men and four women was 65 (39 to 86). Hiatal hernia was present in 25 patients and gastro-esophageal reflux also in 25. Barrett's oesophagus has been previously diagnosed and monitored in five patients. Preoperative radio-chemotherapy was given to four patients. Surgical procedures included 39 Ivor Lewis, four transhiatal esophagectomies and one total gastrectomy.
Results: Thirteen cancers were spread over the entire Barrett's oesophagus, seven were located at the upper end and 23 in the two lower thirds. Twelve tumours were staged T1, five T2 and 25 T3 with 48 per cent N+ tumours. Severe or moderate dysplasia was found around the cancer in 17 resected specimens. Two patients died postoperatively. Among Ivor Lewis operations 32 out of the 39 patients had no complications. The 5-year actuarial survival is 24 per cent.
Conclusion: Total resection of the Barrett's oesophagus is essential in order to remove surrounding dysplasia. A two field oesophagectomy allows thoracic and abdominal lymph node resection.

Flow cytometric DNA analysis and p53 protein expression show a good correlation with histological findings in patients with Barrett's oesophagus

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Introduction: There is a considerable degree of subjectivity and, therefore, substantial inter-observer and intra-observer disagreement in the diagnosis and grading of dysplastic lesions in Barrett's oesophagus. The aim of this study was to evaluate the usefulness of DNA flow cytometry and immunohistochemical staining for p53 protein as objective methods to complement the conventional histological diagnosis of dysplasia in this disease.
Methods: Formalin-fixed, paraffin-embedded tissue of 55 patients diagnosed of Barrett's oesophagus were processed for flow cytometric measurements (ploidy, proliferation index) and p53 immunostaining.
Results: Both the proliferation index measured by flow cytometry and the positivity of the staining for p53 showed a statistically significant increase throughout the sequence: no dysplasia – indefinite for dysplasia – low-grade dysplasia – high-grade dysplasia – adenocarcinoma. Only in the samples with severe histological alterations aneuploid cell populations were found. There is also a highly significant correlation between the results of the cytometric study and the positivity in the staining for p53.
Conclusions: The use of these procedures may play an important role in the evaluation of patients with Barrett's oesophagus. If we consider that staining for p53 is technically simple, economical and quick, and represent a procedure available to most pathology laboratories, it seems obvious that the use of this staining must play a role as a biomarker in this disease. We show the possibility of obtaining adequate results for the cytometric analysis with small formalin-fixed, paraffin-embedded biopsies, following a strict protocol for acceptance of the tissue samples and/or histograms obtained.

Flow cytometric DNA analysis and p53 protein expression improve the identification of Barrett's oesophagus patients that require a more accurate endoscopic surveillance

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Introduction: Regular endoscopic surveillance is recommended for patients with Barrett's oesophagus to detect dysplasia and to diagnose carcinoma while it is in an early and possibly treatable stage. However, there are numerous controversial aspects regarding the natural history of dysplasia in this disease. Our objective was to investigate the usefulness of DNA flow cytometry and immunohistochemical staining for p53 protein in order to define subgroups of patients showing similar histological findings but with a different malignancy potential.
Methods: We reviewed the evolutive behaviour of 81 patients with this disease. For the present study we selected 36 of these 81 patients, including all those who at some time in the follow-up had had a diagnosis of dysplasia in any of its grades (*n*=23). Formalin-fixed, paraffin-embedded tissue of these patients were processed for flow cytometry measurements (ploidy, proliferation index) and p53 immunostaining.
Results: Only in the group of patients with 'indefinite dysplasia' we did find statistically significant differences between the samples from patients with and without progression to more severe lesions, as far as both flow cytometry and staining for p53 are concerned.
Conclusions: Our results suggest that these procedures are capable of distinguishing between a real, although incipient, neoplastic process and morphological changes of a reactive or reparative type.

Quality of life and function of the oesophageal substitute after oesophagectomy and oesophago-gastrostomy for oesophageal cancer

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The recently proposed Gastrointestinal Quality of Life Index (GIQLI)[1] was used to evaluate the outcome of subtotal oesophagectomy and gastric pull-up in 45 consecutive patients (33 male, 12 female, median age 64 years), at a median 13 months after surgery. All the patients were recurrence-free; patients with anastomotic stricture were excluded. The GIQLI was based on a questionnaire containing 36 questions, each of which was attributed a score from 0 (=always) to 4 (=never), regarding foregut symptoms (heartburn, regurgitation, dysphagia, belching), as well as physical, emotional, social and therapeutic aspects of postoperative life in these patients. A matched group of 71 healthy subjects (41 male, 30 female, median age 61 years) served as controls. A subset of 15 patients (ten male and five female, median age 64 years), 10 with moderate to severe foregut symptoms and five with no symptoms, was also evaluated by means of endoscopy with oesophageal and gastric biopsies, supra-anastomotic oesophageal pH- and bilirubin monitoring (Bilitec®), gastric bilirubin monitoring, biliary scintigraphy with ^{99m}Tc-HIDA and gastric emptying scan of a semi-solid meal.
Results: The overall GIQLI score did not differ between patients and controls (120·5, r. 92–142, vs 127, r. 86–143, *P*=ns); however, the partial 'symptom' score was lower in patients than in controls (16, r. 9–20, vs 20, r. 12–20, *P*<0·05): 17 out of the 45 patients (38 per cent) were considered as having moderate to severe foregut complaints (symptom score ≤15). The partial score regarding the patients' physical status also differed from controls (*P*<0·04), whereas the emotional, social and therapeutic scores were similar in patients and controls. In the group of patients who underwent functional evaluation, the presence of oesophagitis, gastritis and abnormal acid gastro-oesophageal reflux did not differ between symptomatic and asymptomatic patients, whereas the percentage time of the presence of bilirubin in the intrathoracic stomach and in the oesophagus was significantly higher in symptomatic patients (*P*<0·01): in particular, an abnormal oesophageal exposure to bilirubin was found in eight symptomatic patients, but only in one asymptomatic case (*P*<0·05). An abnormal ^{99m}Tc-HIDA biliary scintigraphy and delayed gastric emptying tended to be more frequent among symptomatic patients, though the difference did not reach statistical significance.
Conclusion: The overall quality of life in patients who undergo subtotal esophagectomy and intrathoracic oesophagogastrostomy for esophageal cancer is good and does not differ from that of healthy controls, although physical performance is impaired and some foregut symptoms are recorded. These symptoms seem to be mainly related to the presence of bile reflux and, possibly, to abnormal gastric emptying.

[1] Eypasch E, *Br. J. Surg* 82: 216–222, 1995.

Treatment of bile leak following laparoscopic cholecystectomy: the significance of the bile duct of Luschka

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Introduction: The treatment of bile leak following laparoscopic cholecystectomy (LC) depends on the severity of the injury and the site of the leakage. Injury can occur to the extrahepatic biliary tree, excessive dissection to the liver bed, to an undiscovered bile duct of Luschka. Another cause is the leak due to insufficient clip application to the cystic duct.
Methods and results: During the period 1991–1996, 11 bile leaks occurred following 2400 successful laparoscopic cholecystectomies. In two cases bile extravasation occurred because of insufficient clip application, and in nine cases minimal biloma and leakage was observed. All leaks had been indicated by the drain, which was routinely inserted in the subhepatic region. Urgent laparotomy and re-ligation of the cystic duct stump was performed in two cases due to clinically manifest bile-peritonitis and diffuse bile collections in the abdominal cavity. In seven cases the clinical observation and follow-up ultrasound examinations proved to be sufficient, the amount of bile leak decreased continuously, and the discharge disappeared 2–3 days following the operation, indicating that the bile leak was due to injury to bile duct of Luschka. In two other cases the leak persisted for 6–7 days, with constant amounts without clinical manifestations of peritonitis, and ERCP showed bile duct of Luschka that communicated with the drain, and bile discharge regressed in 8–9 days postoperatively, and then ceased.
Conclusion: Following LC, the clinical signs, ultrasound, ERCP and the observation of the tendency of bile leak through the drain can determine the tactics to be followed. Whenever manifest bile peritonitis and diffuse fluid collections are present, this indicates a serious injury to the bile ducts or a technical problem with the clips applied to the cystic duct, thus and urgent ERCP and endoscopic sphincterotomy, laparotomy or re-laparoscopy should be performed. Decreasing rate of the leak without signs of peritonitis indicates an injury to a bile duct of Luschka, which can be treated conservatively.

Five years experience with laparoscopic herniorraphy

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We present our 5 years of experience with laparoscopic hernia repair, development of currently used techniques and concepts. From January 1993 to January 1998 we performed 572 laparoscopic herniorraphies in 519 patients. 2/3 of all hernias were indirect, nearly 1/3 direct inguinal. There were only three femoral and two incisional hernias; 9·27 per cent (53) of our patients were submitted to laparoscopy for bilateral hernia and 6·47 per cent (37) for recurrent one. Patients ranged in age from 15 to 84 years (mean 43). At the beginning the technique was used only in limited number of cases particularly lean men with small hernia. Since then we started to practice it routinely and laparoscopy composes now more than 70 per cent of elective hernia surgery. We encountered no complication requiring laparotomy. We had three cases of intraoperative complication – transection of inferior epigastric vessels. In two patients we successfully stopped bleeding laparoscopically by clips application, one required 3 cm incision in groin area with open ligation of bleeding vessel. In the majority of patients the postoperative period was smooth and uneventful and they were able to regain normal activity after suture removal. Postoperative complications were infrequent and in most cases minor and self-resolving like transient hyperestesia, pain, haematoma or seroma in the groin area. In nine patients seromas had to be drained percutaneously in 1–8 sessions. We observed 23 (4·02 per cent) recurrences. Almost all of them appeared within 1 year after operation. Most recurrences come from a period of time when we used small mesh covering only existing abdominal wall defect. The currently used modified technique with extensive tissue dissection and mesh covering whole groin area is associated with markedly lower recurrence rate. Even though we think that every patient with primary, single hernia is a good candidate for laparoscopic repair, in case of bilateral or recurrent hernia laparoscopic herniorraphy should be particularly recommended.

Does laparoscopic ultrasound identified lymph node status of upper gastro-intestinal malignancy have prognostic value?

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Aim: We have previously shown that laparoscopy, combined with high frequency, high resolution ultrasound improves staging of gastro-oesophageal malignancy when compared to conventional techniques (clinical, endoscopy, abdominal ultrasound and CT scans). This study examined the impact on tumour recurrence and patient survival of intra-abdominal lymph node status identified by laparoscopic ultrasound (LUS).
Materials and methods: Forty-four patients with tumours, deemed resectable, by conventional staging, who underwent LUS, were available for follow-up. Thirty-seven had proceeded to resection and seven underwent palliative therapies having been 'upstaged' by LUS. Data regarding LUS nodal staging, tumour recurrence and patient survival were prospectively collected. All patients were reviewed until death or at least one postoperative year. Nodal group comparisons are between tumours staged N_0 compared with N_1 or 2 by UICC criteria (1992).
Results: Overall there was a 58 per cent 1-year cumulative survival (median 14 months; standard error [SE] 0·08). However, those patients proceeding to resection had 67 per cent 1-year survival (median 17 months; SE 6) which was greater than the palliative therapy group, with no 1-year survivors (median 4 months; SE 6). LUS defined nodal status predicted no significant difference in survival of the overall group or gastric/oesophageal subgroups. However, there was a trend towards prolonged survival in the node negative group (median 29 months; SE 9 compared with 13 months; SE 4 in the positive group). Disease-free survival was greater in LUS node negative patients (26 months; SE 2 compared with 13 months; SE 4; $P<0{\cdot}005$).
Conclusion: LUS staging allows us to predict the likelihood of recurrence of gastro-oesophageal malignancies. This may prove a useful tool for the appropriate allocation of patients to primary and adjuvant therapies.

Open vs laparoscopic Heller-Dor procedure for oesophageal achalasia: a comparative functional study

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Aim: To compare the clinical outcome and the functional results of laparoscopic vs 'open' Heller-Dor procedure.
Material and methods: Our series consists of 30 patients affected by primary oesophageal achalasia; preoperative oesophageal manometry confirmed the diagnosis in each case. All patients underwent laparoscopic (10 patients, A-group) or 'open' surgical treatment (20 patients, B-group). Clinical outcome and functional results were evaluated in all patients, by means of clinical interview, oesophageal manometry and 24-hour pH-monitoring, 6 months after surgery.
Results: Excellent (no food regurgitation or dysphagia) or good (no food regurgitation, dysphagia less than once weekly) clinical outcome was observed in 90 per cent of A-group (9/10 patients) and in 95 per cent of B-group (19/20 patients). One patient for each group had a slight dysphagia but ate an unrestricted diet.

	Preoperative LES pressure (mean±SD)	Postoperative LES pressure (mean±SD)	TRT % (mean±SD)
A-Group	42·0±12·8 mmHg	18·2±3·7 mmHg	1·6±2·0
B-Group	39·2±15·5 mmHg	13·2±5·4 mmHg	3·2±5·7

A statistically significant postoperative reduction of lower oesophageal sphincter (LES) basal pressure was observed in both groups (A-group, $P<0.0001$; B-group $P<0.0001$). Postoperative LES basal pressure was higher after laparoscopic treatment than after 'open' approach ($P=0.01$).

Similar incidence of postoperative pathological reflux (Total Reflux Time [TRT] >3·4 per cent) was detected by 24-hour pH monitoring (A-group 3/10 patients, 30 per cent; B-group 4/20 patients, 20 per cent). A lower mean value of TRT was detected in laparoscopic group, although it was not statistically significant.

Conclusions: Our results confirm that clinical outcomes of laparoscopic and 'open' surgery for oesophageal achalasia are comparable. Both approaches were able to strongly reduce preoperative LES basal pressure with a similar incidence of postoperative pathological reflux at 24-hour pH-monitoring. The higher postoperative LES basal pressure and the lower TRT mean value after laparoscopic treatment could be explained by a much less mobilization of the gastro-oesophageal junction than in the traditional approach.

Preperitoneal laparoscopic hernia repair: totally extraperitoneal (TEP) or transabdominal (TAPP) approach?

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Aim: To evaluate our results in preperitoneal laparoscopic hernia repair with two techniques used: transabdominal approach (TAPP) vs totally extraperitoneal (TEP).

Material and methods: Since November 1993 to December 1997 163 laparoscopic hernioplasties have been performed in 125 patients. Thirty-eight of them had bilateral hernias and 27 (16·6 per cent) patients had recurrent hernias. The median age was 52·2 years (25–76). In 95 cases TAPP was the approach employed and TEP was used in 68.

Results: The median operative time in TAPP was 59·3 minutes (40–150 minutes) and 55·5 minutes in TEP, but the type of hernia, peritoneal tear and the learning curve has a significant influence in TEP's longer surgery time ($P<0.05$). Complications were reported in five TAPP (5·2 per cent) and four TEP (5·8 per cent); mainly local haematomas. Conversion was needed in three TAPP (3·1 per cent) for technical difficulties and seven TEP (10·1 per cent) due to peritoneal tears in six cases and haemorrhage in the other patient; open surgery was used in four cases and TAPP in the other three patients. There were five recurrences (3 per cent): three TAPP finished the learning curve (big direct hernias) and two TEP in the initial learning period of this procedure (missed hernia sac). Day surgery was used in 92·8 per cent of cases.

Conclusions: The results of laparoscopic hernioplasty are similar to open surgery, with painless and short postoperative recovery. We prefer TEP approach because is based in classic preperitoneal precepts. Although technically more difficult, it avoids the potential risk of damaging intra-abdominal organs, vasculary injury or pneumoperitoneum, and spinal anaesthesia can be used.

Colectomies for patients over 80 years old: prospective comparison with a younger population

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The aim of laparoscopic approach is to speed recovery in the postoperative period. A prospective trial was conducted to assess the postoperative recovery after laparoscopic colectomies for patients over 80 years old (group A) and this population was compared with younger population (group B). All patients had a laparoscopic approach for colectomies except carcinoma Dukes A, B and C in group B. Eighty-six consecutive first patients were operated: 26 in group A (80 to 104 years old), 60 in group B (28 to 79 years old). The ASA score was 2·07 in group A (age criteria excluded) against 1·7 in group B (non-significant: NS for $P<0.05$). In group A, 10 patients were ASA 3 or 4 (nine in group B: NS). Indications were group A: 16 cancers, three sigmoidities, four polyps, two prolapses, one volvulus; for group B: 17 cancers, 25 sigmoidities, 15 polyps, two ischemias, one recto-vaginal fistula. Operative procedures were in group A, 15 sigmoidectomies, eight right colectomies, three for left angulus or transverse; in group B: 39 sigmoidectomies, 11 right colectomies, four for left angulus or transverse, six anterior resection or amputation of rectum. No significant difference was found between the two groups according length of resection (17·6 cm in group A against 16·08 cm in group B), conversion rate (23 against 15 per cent), length of procedures (137 minutes against 143 minutes), operative mortality (11·5 per cent against 6·6 per cent), surgical reintervention (3·8 against 15 per cent), the postoperative day for removal of nasogastric tube (3·3 against 3·11 days), day of postoperative recovery (not any tube or drainage: 7·88 days against 8·03 days), day of going home (14·3 days against 12·7 days). These results suggest that there is no age limit for laparoscopic approach for colectomies.

Laparoscopic adrenalectomy – standard treatment of the adrenal tumours

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Aim: Is laparoscopic adrenalectomy safe and effective procedure for adrenal tumours including tumours larger than 4 cm? How many trocars are necessary to perform safe laparoscopic adrenalectomy?

Materials and methods: Forty-one patients who underwent adrenalectomy for adrenal tumours during period 1992–1997. Twenty-five conventional adrenalectomies, nine laparoscopic adrenalectomies in initial period using five trocars (only tumours smaller than 4 cm), seven laparoscopic adrenalectomies in advanced period using three (or four) trocars (also tumours larger than 4 cm). Comparison of mortality, morbidity, time of operation, rate of conversion and hospital stay between three periods of adrenal surgery: conventional, initial period of laparoscopic surgery, advanced laparoscopic surgery.

Results: Average duration of operation: conventional – 90 minutes, initial period of laparoscopy – 120 minutes, advanced period of laparoscopy – 80 minutes. Mortality: 4 per cent (one patient), 0 per cent, 0 per cent respectively. Morbidity: 8 per cent (two patients), 0 per cent, 0 per cent, respectively. Postoperative hospital stay: 9 days, 5 days, 3 days, respectively. Conversion: initial period – 22 per cent (two patients), advanced period – 0 per cent.

Conclusion: During the advanced period of laparoscopic adrenalectomy we proved that this procedure is safe and effective for also small adrenal tumours and tumours larger than 4 cm. It can be done safely using only three trocars in left-sided and four trocars in right-sided adrenalectomy.

Endoscopic papillotomy – when is surgical aid needed?

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The ever-growing improvements in endoscopic techniques have made it possible to approach the common bile duct without surgical intervention, and thus have initiated a new stage in the treatment of the biliary tract and pancreas diseases. The aim of the study was assessment of papillotomy complications with a need for surgical aid. In the years 1987–1997, in the Endoscopic Laboratory (995) endoscopic papillotomies were performed: 647 in choledochal calcinosis, 148 in stenosis of the Vater's papilla, 66 in acute pancreatitis, 61 for exploratory purposes, and 73 in chronic pancreatitis. At that period of time 31 complications developed that required surgical intervention: acute pancreatitis in 21 cases, bleeding in two patients with indications for surgical aid and in seven treated conservatively, restenosis of papilla in six cases, and Dormia's basket impaction in two cases. Four patients in all died: three in the course of acute pancreatitis, and one from myocardial infarction. Diagnostic difficulties and criteria as well as the methods of surgical management in these patients are discussed.

The authors are of the opinion that endoscopic papillotomy constitutes a remarkable advance in the treatment of the biliary tract diseases, but that it should be done by highly skilled endoscopists cooperating with surgeons sensitized to the early diagnosis of possible complications and to their early effective surgical treatment.

Transanal endoscopic microsurgery (TEM): technical changes towards a one-surgeon procedure

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Aim: Technology which has been used in the operating room often with little regard to the cost, is emerging now as a help on providing quality care at lower cost. In fact, minimal invasive surgery is moving to the 'solo' surgery conception which would reduce hospital cost by both shortening surgical case time and increasing staff productivity. Transanal Endoscopic Microsurgery (TEM), a world-wide recognized technique for the local treatment of rectal tumours, was conceived as a two-people procedure mainly as a way for direct training. This paper presents the changes introduced to facilitate TEM as a one-surgeon technique.
Material and method: In January 1996 we started working on the one-surgeon TEM technique. First studies lead us to design a new suction device to be used with the right hand. The prototype was tested on laboratory pigs, performing both mucosectomy and full-thickness resection. These experiences served to develop the final version of the suction device as well as the concept to its use.
Results: The new catheter was clinically applied in July 1996. Since then, we have used it on 12 rectal tumours. Results regarding both operating time and blood lost were similar to those offered by the two surgeon technique.
Conclusions: Only minor changes were required to facilitate TEM to be performed just for one surgeon. In the competitive health care environment, we need to continue to explore new types of technology to help us maintain quality while lowering costs.

Gasless and CO_2 pneumoperitoneum laparoscopic surgery: a prospective and randomized study

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CO_2 pneumoperitoneum induces respiratory and haemodynamic changes which may be problematic for patients with high risk of developing cardiopulmonary complications. Gasless laparoscopic surgery would be an alternative route to avoid deleterious effects inherent to pneumoperitoneum. The purpose of this study was to compare perioperative and postoperative disturbances in patients who underwent laparoscopic cholecystectomy, gasless and under pneumoperitoneum.
Patients and methods: The effects of both procedures were studied in 60 patients undergoing laparoscopic cholecystectomy, who were randomly assigned in two groups: Group A – 30 patients in whom the operation was carried out under CO_2 pneumoperitoneum; and Group B – 30 patients undergoing gasless laparoscopic cholecystectomy. Mean operative time and mean blood loss were similar in both groups. Several parameters were registered preoperatively, perioperatively and postoperatively: pulse rate, arterial rate, arterial blood pressure, central venous pressure (CVP), arterial oxygen tension ($PaCO_2$), CO_2 arterial ($PaCO_2$), arterial pH, % O_2Sa and End-Tidal CO_2.
Results: We noticed significant decrease in pH values and pulse rate (postoperatively), increase in $PaCO_2$ and CVP (perioperatively), and increase in End-tidal CO_2 (perioperatively and postoperatively) in the group A, which were statistically significant ($P<0·05$).
Conclusions: As alterations under gasless laparoscopy are significantly fewer than after pneumoperitoneum they provide objective support for performing gasless approach in patients at high risk for developing cardiopulmonary complications, for whom CO_2 pneumoperitoneum may be a contra-indication.

Minilaparoscopy in abdominal malignancies

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Current experience indicates that laparoscopy is an important tool for the evaluation of patients with malignant abdominal disease.
Materials and methods: In order to determine the reliability of minilaparoscopy for diagnosing, staging and restaging abdominal malignancies, 61 patients were evaluated using a 2 mm instrument (Auto Suture, USSC) in an endoscopy suite, under conscious sedation (5–10 mg of diazepam) and local anaesthesia (10–20 ml of mepivacaine 1 per cent). The procedure required the insertion of two small diameter trocar sites and only 1·0–2·0 l nitrous oxide to obtain adequate pneumoperitoneum.
Results: In 17 patients the procedure was performed with diagnostic purpose. Out of six women with a pelvic mass, ovarian cancer was diagnosed in five, and myoma in one. Among 11 patients with ascites of unknown origin we diagnosed a mesothelioma in five, an ovarian cancer in two, a pseudomyxoma in one, and metastases from breast cancer in three. In nine patients the procedure was performed to stage digestive tumours. Out of seven patients with gastric cancer, six revealed clinically evident ascites, and in one ascitic fluid was detected by endosonography. The remaining two patients with ascites were affected by HCC. In all patients minilaparoscopy demonstrated peritoneal spread. In 35 patients the procedure was performed to restage ovarian cancer. Positive macroscopic findings were confirmed by cyto-histological samples in 13 cases: in these patients serum marker level was normal. In 22 cases laparoscopy and cyto-histologic samples were negative: the serum marker level was normal in these patients too. Two of them were submitted to surgical removal of a retroperitoneal and a vaginal lesion, respectively: in these cases surgery confirmed the absence of endoperitoneal malignancy. Neither complications occurred, nor adhesions limited exploration of the abdominal cavity. In all cases, the discomfort was minimal during laparoscopic procedure, and absent in the following 24 hours. In this period after laparoscopy, no patient required analgesic drugs. With regard to impact on treatment, minilaparoscopy prevented surgical exploration in 54/61 patients and modified therapeutic approach in 16 cases (surgery → definitive or neo-adjuvant chemotherapy).
Conclusions: In our experience, minilaparoscopy seems to be a safe and reliable procedure for diagnosing, staging and restaging abdominal malignancies, with optical performance similar to that of conventional instruments, minimal, if any, discomfort for the patients and significant role in the management of oncological patients.

Laparoscopic treatment of hiatal hernia

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Introduction: In our opinion the surgical treatment of the gastro-oesophageal reflux should be done nowadays by laparoscopy which permits the performance of the same operations and decreases the surgical trauma.

Patients and methods: During the last five years we have performed 92 laparoscopic operations for treatment of hiatal hernias. All of them presented with a long history of gastro-oesophageal reflux and upper gastrointestinal haemorrhage episodes with non-satisfactory response to medical and postural treatment. Eighty-seven patients had a moderate-severe oesophagitis (grade I-II in 50 cases, III in 19 cases, and IV in 18 cases), showed pathologic gastro-oesophageal reflux (mean % time pH<4·20, mean De Meester score 72·5, mean episodes over 5 minutes, nine) and low rate of LESP (mean 6·3 mmHg) according with their hiatal hernia. Average time of surgery was 134 minutes. One conversion to laparotomy (1 per cent) was necessary because of arterial bleeding. The surgical technique was always similar, using five ports. In all cases the hiatus was narrowed, calibrating with a 50 F oesophageal tube in 64; 89 Nissen-Rossetti fundoplications were performed in a length around 2·5–3 cm and two Dor fundoplications, one case because of motor oesophageal disorders that dissuaded us from a complete fundoplication and in the other because of technical troubles.

Results: Postoperative recoveries were uneventful (mean postoperation stay of 2·4 days). Forty-five cases complained of mild solid dysphagia that disappeared between 15 and 120 days. pH recordings and manometries made between two and four months after surgery in 54 cases showed no gastroesophageal reflux and high LESP (16 mmHg of mean). After 3 months 77 per cent of patients were asymptomatic, and after 1 year this rose to 91 per cent.

Conclusions: From our experience, we feel that the results are comparable to those obtained with the open technique, with a reduction in surgical sequelae.

Double-stapled anastomosis after anterior resection for rectal cancer

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Aim: A consecutive series of patients submitted to low anterior resection with double-stapled anastomosis below the pelvic peritoneum has been prospectively evaluated to identify the surgery-related risk factors influencing anastomotic complications.

Materials and methods: Between November 1994 and August 1997, 115 patients (60 men, 55 women) with a mean age of 69·3 years were operated on for rectal cancer. The site of lesion was the rectal-sigmoid junction in 41 patients, the upper rectum in 37 and the middle-lower rectum in 37. Preoperative radiotherapy and chemoradiotherapy was delivered in 11 and four cases respectively, with a mean radiation dose of 4000 Gy.

Splenic flexure mobilization, inferior mesenteric lymphoadenectomy and total mesorectal excision for extraperitoneal rectal cancer were routinely carried out. A protective colostomy was performed in 7/105 patients who underwent elective surgery and in 10 patients who had emergency surgery.

Results: Postoperative mortality was 3·5 per cent (four patients). A radiological leak was detected in three (2·6 per cent) patients, a clinical leakage was observed in three (2·6 per cent) patients with no leak-related death or peritonitis. Furthermore, one colovaginal fistula and one anastomotic haemorrhage were reported. Four (3·5 per cent) patients developed an anastomotic stricture, treated by serial mechanical dilatations.

The incidence of anastomotic complications was significantly increased when anastomotic height was less than 6 cm from the anal verge ($P<0·05$). Leak rate appeared directly related to the proximal extent of colonic resection ($P<0·05$). No significant relationship to age, sex, tumour stage, neo-adjuvant treatment, emergency or elective surgery was found.

Conclusions: Double-stapled technique is reliable and safe. Surgical risk factors include the proximal and distal extent of colorectal resection. This study suggests that a diverting stoma is rarely required.

The role of local excision for rectal cancer

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The aim of this retrospective study was to evaluate the results of local excision (LE) for rectal cancer for curative purposes and to compare them with those achieved after abdominoperineal resection (APR) and sphyncter saving resection (SSR).

From 1969 to December 1997, a total of 456 operations were performed for surgical treatment of rectal carcinoma (262 males and 194 females, mean age 66 years). Twenty patients underwent LE, seven males and 13 females, median age 65 years. Patients were selected for LE if they met the following criteria during preoperative staging: tumours staged as T_1, N_0, M_0 with a distance from anal verge <10 cm, grading G_1 or G_2, size <3 cm, not ulcerated. Preoperative evaluation included a colonscopy with biopsy, transrectal ultrasonography, a barium enema and in some cases a pelvic TC. As far as the type of LE is concerned, we performed 13 transanal excisions (Francillon technique), two Mason, three endoscopic excisions and two TEM. In patients who underwent TEM the tumour was located at 8 and 10 cm from anal verge.

Among patients who underwent LE there was no operative mortality. Thirteen tumours were T_1 and seven were T_2: pathologic findings included 20 adenocarcinoma, 13 G_1 and seven G_2. There was no postoperative specific morbidity, while aspecific morbidity was minimal (5 per cent) including one pneumonia. There were no local recurrences but two patients (10 per cent) had secondary lesions. Five-year overall survival after LE was 88·4 per cent. Comparing T_1 and T_2 tumours after APR and SSR (17 T_1 and 44 T_2, all adenocarcinoma), operative mortality, specific and aspecific morbidity were respectively: 1·6 per cent ($P=0·56$), 19·6 per cent ($P=0·031$) and 11·7 per cent ($P=0·38$). There were five (8·3 per cent) local recurrences ($P=0·18$) and five (8·3 per cent) metastatic lesions ($P=0·81$). Five-year overall survival was nearly the same as LE (82·8 per cent with $P=0·63$).

LE for rectal carcinoma can be performed in selected patients provided there is correct preoperative staging. Five-year overall survival, local recurrence and operative mortality were similar to APR and SSR, while there was an improvement in results after LE in terms of specific morbidity.

Total mesorectal excision for the surgical treatment of rectal cancer

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The aim of this study was to retrospectively evaluate the results of two groups of patients admitted and treated for rectal cancer in our Institution. From 1980 to 1992, 198 patients were admitted and operated for cancer of the rectum. Forty-seven were lost to follow-up and 151 patients were available for evaluation. The patients admitted and treated from 1980 to 1987 (80 patients, group A) were radically operated with standard technique, patients operated from 1988 to 1992 (71 patients, group B) underwent total mesorectal excision (TME). Mean follow-up was 73·5 months. Groups were similar according to demographics, staging and pathological data.

Results: No operative mortality was observed in this series. Complications were observed in 12 patients (15 per cent) in group A and in 23 patients (32 per cent) in group B. Local recurrences were found in 33 patients (41·2 per cent) in group A and in nine (12·6 per cent) in group B. Distant metastases occurred in 17 (21·2 per cent) and in five (7·6 per cent) respectively in groups A and B. Cancer-related mortality was 62·5 per cent in the non-TME group and 19·5 per cent in TME group. Overall 5-year survival was 32·4 per cent in group A and 70·5 per cent in group B. Disease-free survival was 25 per cent and 62·3 per cent in group A and B respectively. From the results of our study, it can be concluded that TME seems to lower the incidence of cancer-related mortality, with a higher incidence of postoperative complications. Further studies need to be done to assess the real benefits of TME in the surgical treatment of rectal cancer.

Emergency presentation of colorectal malignancies: experience of an emergency surgery unit

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To assess the incidence of large bowel cancer as a casue of abdominal surgical emergency, our series of 2745 consecutive patients referred to the Emergency Surgery Unit of the University Hospital over a 2-year period (October 1995–October 1997) was retrospectively reviewed. The Unit collects patients from a population area of about 200 000 people. Only those patients were considered who had non-traumatic abdominal emergencies. Two hundred and one patients were admitted for an acute presentation of a large bowel disease, 125 of them had cancer; there were 67 males and 58 females, mean age was 71·5 (SD: 11·11). Presentation of the neoplastic disease was with intestinal obstruction in 68 cases, peritonitis due to colonic perforation in 10, rectal bleeding in 25, acute abdominal pain in 21 and vesicoenteric fistula in one. The tumours were more frequently located in the sigmoid colon (35 cases) and the rectum (34), while caecum and descending colon were the least common sites (respectively 14 and nine cases). One hundred and twenty three emergency procedures were carried out on these patients, as two of them died before surgery. The tumours were mainly advanced (Dukes C: 118 cases; Dukes B: three cases; Dukes A: four cases) with seven cases of diffuse periotoneal cancer implantation, and five of infiltration of other organs. Colonic resection was performed on 106 patients while 17 patients had intestinal by-pass procedures or colostomy becasue of too advanced disease or poor general conditions. Operative mortality was observed in four cases (3·2 per cent). Thus, large bowel tumours were responsible for 4·5 per cent of all the abdominal emergencies; they also accounted for 35·4 per cent of all intestinal obstructions, 10·8 per cent of peritonitis and 55·5 per cent of rectal bleeding episodes observed during two years of activity.

Whereas great emphasis is posed on the early diagnosis of colorectal malignancies, they still represent a common indication for emergency surgery. These data confirm the need of a more intensive surveillance, particularly in older people, on early symptoms of large bowel cancer.

Implementation of a policy of preoperative radiation therapy and total mesorectal excision in rectal cancer treatment

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Introduction: Surgical treatment of rectal adenocarcinoma is followed by local recurrence in as much as 30 per cent of patients, resulting in significant morbidity. Recently, preoperative radiation therapy (RT) has been shown to improve local recurrence rates as well as long-term survival. We prospectively evaluated the value of preoperative RT followed by total mesorectal excision (TME), which is considered to be the current standard in rectal cancer surgery.

Patients and methods: Thirty-one patients were treated in a four-year period. Mean age was 60 (range 56–65); 19 (61 per cent) were male. Seventeen (55 per cent) patients had a low tumour (0–5 cm). All patients underwent short-term hyperfractionated RT (total dose: 41·6 Gy) immediately followed by surgery. Sphincter-preserving surgery was performed in 19 (61 per cent) patients. Mean follow-up was 23 months.

Results: UICC Stage distribution was as follows: Stage O: one (4 per cent); Stage I: 10 (32 per cent); Stage II: eight (26 per cent); Stage III: 10 (32 per cent); Stage IV: two (6 per cent); two patients had R2 resections (liver metasases). There was no in-hospital mortality. RT was reasonably well tolerated by most patients; five patients (16 per cent) developed serious side-effects: rectovaginal fistula (2); radiation colitis (2) and subobstruction by adhesions (1). No anastomotic leaks were seen. Mean overall survival was 39 months; Kaplan–Meier analysis resulted in survival after one and three years of 91 per cent and 79 per cent respectively for R0 resections. Local recurrence developed in two (6 per cent) and isolated distant recurrence in two (6 per cent) patients operated on with curative intent.

Conclusion: The combination of preoperative RT and total mesorectal excision resulted in excellent figures for local recurrence rate and intermediate-term survival; long-term follow-up is needed to confirm our present findings. Toxicity of the RT regimen remains worrysome, but will probably diminish with increasing technical expertise.

Prognostic value of DNA ploidy in patients with B and C Dukes colorectal carcinoma

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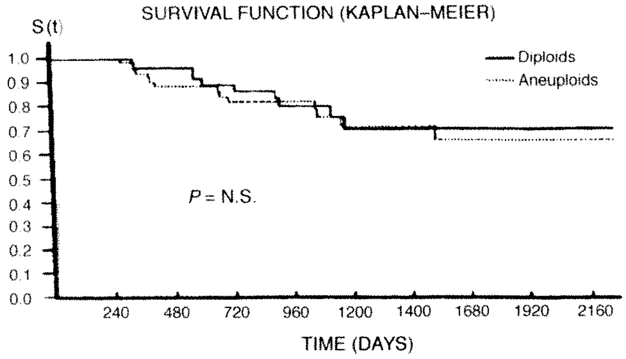
Aim: To determine the value of DNA ploidy in the prediction of recurrence in colorectal carcinomas.

Patients and methods: Curative resection was performed in 123 unselected patients with B and C Dukes colorectal carcinomas. Flow cytometry of DNA (CF) was performed in fresh specimens at time of resection. Patients were followed until the end of 1996 when the present study was closed. Recurrence was analysed by Cox's proportional hazard regression model. The presentation of recurrence was considered the event and follow-up was defined as time elapsed between intervention and last revision or the presentation of recurrence. Significance was performed by log rank test.

Results: Twenty-five recurrences were detected (16 in rectal cancer and eight in colon cancer). Seventy-one carcinomas (58 per cent) were found to be aneuploid and 52 diploid. Neither ploidy nor data of cell cycle (G_0/G_1, S and G_2/M) were found to be significantly correlated with the recurrence.

Conclusions: No flow cytometry data could significantly improve the prediction of recurrence.



Lack of genetically detected circulating tumour cells render the 'no-touch isolation technique' unnecessary in colorectal cancer

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Aim: The benefits of the 'no-touch isolation technique' usually carried ou to prevent the circulation of tumour cells are not evident. The aim of thi study was to determine whether conventional surgical procedures fo treatment of colon cancer could provoke the circulation of tumour cell detected by a genetic technology.

Methods: Fifteen patients undergoing resection for colorectal cancer an two patients with irresectable tumour were studied. No patient showe liver or lung metastasis. With specific primers for carcynoembryonic antigen (CEA), we used the reverse transcriptase-polymerase chain reactio (RT–PCR) to analyse tumour biopsy specimens and blood sample obtained from the antecubital vein prior to and after surgery and from th main drainage vein of the tumour when the tumour was being extracted Peritoneal fluid was also collected in irresectable cases.

Results: Amplification of cDNA with the primers specific for CEA specific primers was achieved with all tumour biopsies and samples o peritoneal fluid. In two patients CEA RT–PCR products were detected i antecubital vein prior to surgery and in one of them also after surgery Only in one patient (Dukes C) CEA RT–PCR products were detecte from the main drainage vein of the tumour. In serial dilution experiments we determined that limit of detection of this method was 10 tumour cell in 2 ml of blood.

Conclusion: Our results indicate that in the vast majority of patients les than 10 viable tumour cells are present in 2 ml of blood before surgery and that this number does not increase by performing standard surgica procedures to remove colorectal tumours. According to the no-touch isolation theory, this is the time when the probability of the tumour cell spread should be maximal. Our data suggest that the use of 'no-touc isolation techniques' in colorectal cancer is not justified, based on lack o evidence indicating the detachment of cells from the tumour upo surgery.

Results of endoscopic ultrasonography in preoperative detection of nodal metastases from rectal cancer

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Preoperative staging of rectal cancer is crucial to assess an appropriate therapeutic approach. Among all imaging modalities, endoscopic ultrasonography (EUS) is commonly considered as an accurate method of assessing tumour infiltration and lymph-node involvement. Perirectal metastastic lymph-node can be identified with reported sensitivity and specificity of approximately 80 per cent[1]. Recently it has been shown[2] that even the manual dissection instead of the clearing technique of the mesorectum can demonstrate metastases in approximately 50 per cent of the lymph-nodes smaller than 5 mm. Aim of this study was to analyse our experience with EUS in rectal cancer, relating our results to the technique used for pathological detection of lymph-nodes.

Materials and methods: From April 1991 to December 1997, 146 patients with rectal cancer, undergoing curative surgery without radiotherapy, were staged preoperatively by means of EUS. Endosonography was performed using Olympus GF-UM3/UM20 and CF-UM20 mechanical radial scanning echoendoscopes (frequency 7·5/12 or 7·5 MHz, scanning angle 360 or 300°). Seventy-eight specimens were examined by different pathologists with different experience, 68 by the same pathologist with particular interest in this disease. Statistical analysis was performed using the z-test, at the 5 per cent significance level ($z>1{\cdot}96$).

Results: Diagnostic accuracy of EUS for nodal staging significantly decreased according to pathological technique and incidence of metastases in lymph-nodes <5 mm. The results for the two groups of patients were the following: overall accuracy (78·2 per cent vs 47·1 per cent [$z=3{\cdot}98$]), sensitivity (70·9 per cent vs 27·7 per cent [$z=3{\cdot}52$]), specificity (79·6 per cent vs 68·7 per cent [$z=1{\cdot}14$]), positive predictive value (68·7 per cent vs 50·0 per cent [$z=1{\cdot}37$] and negative predictive value (81·2 per cent vs 45·8 per cent [$z=5{\cdot}31$]).

Conclusions: Although EUS is a reliable and highly accurate method for preoperative nodal staging of rectal cancer, the results are related to the technique used by the pathologist when dissecting the surgical specimen.

1 Mehta et al., Clin. Radiol. 1994, 49: 515–523
2 Andreola et al., Cancer 1996, 77: 607–612

Virtual colonoscopy in the diagnosis and staging of colorectal neoplasms

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Aim: The purpose of this work is to demonstrate the level of detail and diagnostic possibilities of three-dimensional CT of the colon in patients with colorectal tumours and to compare the results with barium enema, fibreoptic endoscopy and operative results.

Materials and methods: Thirty-six patients (47–78 years, 16 female, 20 male) with suspected colorectal tumours underwent 3D CT colonography, fibreoptic endoscopy and double contrast barium enema examinations. The examinations were performed within a 3-day period. For 3D CT colonography, the colon after cleaning was retrogradely insufflated with air and iv. peristalticolyticum was given. A 45 second spiral, thin collimation scanning was performed during breathhold. A second spiral scan was added at the region of interest with i.v. contrast material. From these data 3D images and virtual colonoscopy simulations were generated on a separate graphic workstation. Views from outside, from inside, surgically opened views and holographic views were produced for preoperative assessment. The results were compared with those of fibreoptic colonoscopy, barium enema and biopsy.

Results: Virtual colonoscopy detected all 17 malignancies diagnosed by colonoscopy. Two additional higher tumours were diagnosed by virtual colonoscopy (and barium enema) not reached by partial colonoscopy. In detecting polyps, CT colonography was 100 per cent sensitive for polyps >20 mm, but only 60 per cent sensitive for polyps <20 mm. On CT scans used for virtual colonoscopy generation, the transmural extent and lymph node involvement of the tumour was well evaluable.

Conclusions: Virtual colonoscopy minimizes patient discomfort and inconvenience and seems to be a useful diagnostic modality in detecting and staging colorectal neoplasms. In virtual colonoscopy the right side of the colon can always be reached. For screening purposes technical refinements are needed to increase sensitivity for small polyps.

Laparoscopic transabdominal preperitoneal (TAPP) technique in the treatment of groin hernias

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There are several techniques for laparoscopic repair of inguinal hernias. Only two of these spread in the clinical practice; implantation of a mesh through transabdominal preperitoneal and total preperitoneal way, all of the others did not become generally used operation because of their complications and unacceptably high recurrence rate. In two departments 200 laparoscopic hernia repair have been performed at 165 patients by TAPP technique for three and a half years. Thirty-three patients (21·2 per cent=35/165) had bilateral hernias, and the indication of surgery was recurrent hernia after traditional herniorraphy in 67 cases (=33·5 per cent). Femoral hernias were operated on at three female patients. There were no intraoperative complications except damage to epigastric vessels in two cases which were easily managed through laparoscopy. Postoperative complications included three (1·5 per cent) hydroceles, nine (4·5 per cent) spontaneously resolving neuralgia and one (0·5 per cent) umbilical trocar hernia. All of the seven (3·5 per cent) recurrent hernias were developed during the first (1–4 months) after surgery, and were able to be explained with the lack of skill. There was only one recurrence from the last 100 cases. The advantages of the operations are the minimal postoperative pain, the lack of wound infections, early return to the normal activity (1–2 weeks after surgery) and in particular the more favourable conditions in the treatment of recurrent and bilateral hernias.

Calibrated inguinal hernioplasty with multiple plugs (variant of Trabucco repair)

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The authors propose to modify the Trabucco repair in the treatment of primary inguinal hernias, using one or more plugs and a standard double layer polypropylene mesh, fitting its hole to the variable distance of the funiculus from the pubic tubercle. From 1994 to 1997 the authors operated on 636 inguinal hernias distributed, according to Gilbert's classification modified by Rutwok and Robbins, as follows: I – 27 (4·2 per cent); II – 268 (42·1 per cent); III – 110 (17·3 per cent); IV – 06 (16·7 per cent); V – 3 (0·5 per cent); VI – 122 (19·2 per cent). A classic Trabucco repair was performed in 420 cases (66 per cent; in the remaining 216, two, three, four plugs were employed respectively (177, 38 and one case). Multiple plugs were used to reduce voluminous hernia sacs, suturing over them the disrupted fascia transversalis to the iliopubic tract. The calibrated repair was immediately assessed by stress test: 629 patients received local anaesthesia (98·9 per cent), three spinal (0·5 per cent) and only four narcosis (0·6 per cent). All the patients operated on under local anaesthesia ambulated immediately, had a meal shortly afterwards and were discharged within 24 hours. The following parameters have been used to value the method: hospital and domiciliary analgesic requirement (293 and 174 patients, 46 per cent and 27 per cent respectively), postoperative complications (10 patients, 1·6 per cent), driving cars and return to work of self-employed patients within five days (207 out of 248 and 76 out of 115 interviewed). During a 0 to 4-year follow-up, only one recurrence has occurred (0·16 per cent). The proposed technique permits a calibrated reconstruction of the posterior wall, with scanty pain, prompt functional rehabilitation and early return to unrestricted work.

Laparoscopic surgery for huge abdominal hernia: a series of 45 cases

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We report a retrospective analysis of 45 elderly and obese patients between 45–75 years who underwent laparoscopic cure of a huge ventral hernia between January 1994 and January 1997. This technique is perfectly adapted to elderly and obese patients. Complications are less frequent and better tolerated than for conventional open surgery. In this series, the success rate was 93·33 per cent with technique-related complications 5·5 per cent. None of the patients is dead. Three patients developed a later recurrence.

Prosthetic repair of incisional hernias

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In this retrospective study, evaluation of 161 cases of primary or incisional hernia operated by prosthetic repair and long term results of 60 cases were presented. In 74 patients mersilene mesh (Group I), in 74 patients prolene mesh (Group II) and in 13 patients steel mesh were applied. One hundred and forty-seven cases were postoperative ventral, primary umbilical or paraumbilical hernias and six cases were postoperative lumbar hernia. 'Strengthened primary repair' was applied in 153 cases. In eight patients the defect could not be closed primarily. In Group I, complication rate of early period was 17·5 per cent and that of late period was 4 per cent. The recurrence rate was 7 per cent and rejection rate was 6·7 per cent. In Group II complication rate of early period was 10·7 per cent and that of period was 2 per cent. The recurrence rate was 3·2 per cent and rejection rate was 2·7 per cent. Apart from surgical procedures used in recurrent hernias of abdominal wall, when indicated, prosthetic repair is especially useful in cases where tissues are not enough and repair is weak. As a result, we thought that in prosthetic materials, prolene mesh has an advantage over mersilene mesh.

Functional subfascial hernioplasty: a new technique in repairing groin hernias

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Aim: Many procedures have been described to repair groin hernias. The lowest rate of recurrences has been achieved with prostetic meshes. We have developed an alternative procedure for repairing inguinal hernias, using a polypropylene mesh, in retrofascial position, without opening the transversalis fascia and with anatomical reconstruction.

Material and methods: From January 1996 to June 1997, 39 patients with uncomplicated unilateral inguinal hernia were operated on. Local anaesthesia was used in nine cases, general anaesthesia in the other 30. According to the Gilbert–Rutkow classification the group included three type II patients, 15 type III, 21 type IV. One dose of Cefminox (2 g) was administered prior to the operation in all cases.

Anterior approach of the inguinal region. External oblique aponcurosis and cremaster muscle are cut longitudinally following their fibres. The sac is dissected, free of the cord elements, being replaced into the abdominal cavity when medium size and transsected when too large. Direct hernias are dissected and reduced through the internal ring. In none of the cases the transversalis fascia was open. Bogros space is completely shown. A possible femoral hernia is searched for. A polypropylene mesh (8 × 14 cm) is placed through the internal ring, behind the transversalis fascia, leaving a hole for the spermatic cord, like a brace. The most lateral point of the mesh is fastened to the muscular wall with a single non-absorbable stitch performing a Barker manouvre. Transversalis is folded with a continuous suture of non-absorbable material. Each cremaster muscle and external oblique aponeurosis are closed with a continuous absorbable suture.

All patients were followed up for an average time of 14 months (range 4–16).

Results: Haematoma occurred in one patient who was taking AAS. There was no incidence of wound infection, corditis, testicular atrophy or mesh intolerance. The discomfort level, according to an analogic score was mild (3/10). The postoperative recovery was excellent in the 39 cases. We did not find any instances of recurrent hernias.

Conclusions: This is a preliminary study, and more patients with a longer follow-up should be studied. We conclude that the functional retrofascial hernioplasty is useful in the reinforcement of inguinal canal floor, giving it back its dynamic qualities.

Comparative study between stoppa and laparoscopic repair in the treatment of bilateral inguinal hernia

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The study group consisted of 71 consecutive patients, presenting with bilateral hernia, operated on between 1993 and 1996. A Stoppa repair was performed on 37 patients (group S) and a transabdominal preperitoneal laparoscopic herniorrhaphy on 34 patients (group L). The series consisted of 65 men and six women, the median age was 56 years (range: 24–85). According to the Nyhus classification, there were 30 type 2, 77 type 3a, 23 type 3b and 12 type 4 hernias. Preoperative characteristics of both groups were equivalent. All the patients were evaluated in December 1997; the median follow-up was 33 months (range: 12–60). When comparing group S with group L, we noted a similar operative time: 103±24 vs 109±22 minutes (NS) but a longer postoperative hospital stay: 6±2 vs 4±1 days ($P<0{\cdot}001$). The postoperative pain was evaluated by a visual analogue scale (score from 0 to 10) and by the use of painkillers (g of paracetamol). On the first postoperative day, the two parameters were higher in group S; respectively 5·7±1·9 vs 4·7±1·4 ($P<0{\cdot}05$) and 1·7±1·7 vs 0·7±1·1 g ($P<0{\cdot}02$). That difference was no longer noted from the third postoperative day. Significant morbidity occurred in six patients of group S: two orchitis, two wound haematomas, one seroma, one pneumonia and in three patients of group L: one orchitis, one wound haematoma, one seroma (NS). We recorded a slower return to home activities in group S: 8±3 vs 6±2 days in group L ($P<0{\cdot}01$) but, the interruption of professional activities was similar in both groups: 30±10 vs 31±7 days (NS). Finally, we found two recurrences in group S and two in group L (NS). In conclusion, both procedures were associated with a low postoperative morbidity and hernia recurrence rate. We also recorded that laparoscopic herniorrhaphy was characterized by a lower postoperative pain. That advantage, even if limited to the first two postoperative days, induced a shorter hospital stay and a quicker return to current activities.

Recurrence of adult groin hernias five years after repair in a district general hospital

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Background: Little is known of recurrence rates for established methods of inguinal hernia repair in British surgical practice.

Methods: All groin hernias at York District Hospital in the year to 31st March 1992 were identified. Details of patient, hernia and repair were extracted from the casenotes. Recurrence was established by questionnaire, telephone and clinical examination for those who were unsure. Randomly selected patients who were certain that no recurrence had occurred were also invited to attend and 100 of these were examined.

Findings: We identified 554 patients and 604 groin hernia repairs. Seventy-seven notes were unobtainable; 30 patients (31 repairs) were uncontactable, leaving 496 repairs which were assessed for recurrence. Most were inpatient elective repairs of inguinal hernias under general anaesthesia. Fifty-seven repairs were for recurrent hernias. One hundred repairs were for bilateral hernias. Sutured repairs of various types were performed in most cases. The overall recurrence rate was 6 per cent (30 of 497 repairs). The recurrence rate for primary unilateral inguinal hernia was 2·9 per cent (10 of 342). The recurrence rate was significantly worse for recurrent hernias at 19·3 per cent (11 of 54) and for bilateral hernias at 9 per cent (9 of 100) for each groin. Recurrence rates were not significantly different for various methods of repair or for seniority of surgeon. A recurrent hernia was found in 6 per cent (6 of 100) patients randomly invited for examination after reporting no recurrence by questionnaire.

Conclusion: Various repairs give staisfactory recurrence rates for primary unilateral inguinal hernias. These methods are unsatisfactory for recurrent and bilateral hernias. Clinical examination is essential to establish true recurrence rates.

Has the mesh impact on wound healing after abdominal hernia repair?

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Introduction: Incisional hernias are common complications following abdominal surgery. The use of prostheses is indispensable in major anterior abdominal hernias when it is not possible to close the edges of the hernial opening without tension. Despite the advantages of the synthetic meshes, complications after implantation are also reported.

Aim: To assess the incidence of early postoperative wound healing disorders and infections after elective abdominal hernia repairs with and without synthetic mesh implantation in the first four years of our Department.

Materials and methods: From January 1994 to January 1998 at our Institute 178 elective abdominal herniorapphies were performed. The inguinal hernias are not included in this study and the data were analysed retrospectively. Ninety-three incisional hernia repairs were done by preperitoneal technique using non-absorbable surgical mesh (first group). The male:female ratio was 20:73, average age 57 (28–78) years. In the second group (85 patients) conventional closure of the abdominal wall was chosen. The male:female ratio was 21:64, average age 54 (26–84) years. The body mass index (BMI) in the group I, was 34 kg/m^2 by males vs 32 kg/m^2 by females and 29 kg/m^2 vs 31 kg/m^2 in group II. Antibiotic prophylaxis (cephalosporin i.v., for 48 hours) and 48 hours bed rest was used at all patients with mesh implantation.

Results: Postoperative fever (over 38 grade C) occurred in 39 (42 per cent) in the first group vs 16 cases (19 per cent) in the second group. A significant difference was found in the length of surgery: mean operation time 123 minutes (45–240) in group I vs 60 minutes (15–210) in group II. During the early postoperative period (the first 30 days), in group I, wound healing disorders were detected in 11 cases (12 per cent). Eight of them (8·8 per cent) were seroma and necrosis of the skin margin and three of them (3·2 per cent) wound infections. In this group the rate of the diabetic patients was 8·6 per cent, and 37 per cent of them developed wound complications. The synthetic mesh has not required explanation in any case. In the second group there were no diabetic patients, one seroma (1·17 per cent) was found.

Conclusion: In overweight and diabetic patients with incisional hernias there is an increased risk of wound complications when mesh implantation is necessary, although the advantages of modern synthetic meshes are indisputable.

The continuing challenge of parastomal hernia – failure of a novel polypropylene mesh repair

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Aims: Parastomal hernia is a frequent complication of stoma formation which is seen following up to 50 per cent of colostomies and 10 per cent of ileostomies. Although there are many reports of successful repair techniques with excellent short term results, long term follow-up has been less satisfactory. Because of our own poor results with standard techniques, amply confirmed by others, we devised a novel technique, which we hoped might provide an effective barrier to the defect between the abdominal wall and the emerging bowel. We now report long-term results of the technique.

Patients and methods: In the period 1990–1992, seven patients were treated including five paraileostomal and two ileostomal hernias. The new technique involved constructing a fitted internal wrap using two pieces of polypropylene mesh. The meshes were cut to form three longitudinal 'fingers'. The outer 'fingers' were passed around the neck of the sac and overlapped to strengthen the abdominal wall around the defect. The middle 'fingers' were turned inward along the ileum/colon, and sewn together with polypropylene sutures to form a tubular sheath directed along the bowel into the peritoneal cavity for a distance of 3 cm. This sheath was loosely sutured to the seromuscular coat of the bowel, but was sufficiently loose to avoid constriction. The main bulk of each piece of mesh was sewn with interrupted polypropylene sutures to the parietal peritoneum and underlying muscle, ensuring coverage well beyond the margins of the defect.

Results: Five year follow-up has given disappointing results with recurrent hernia in two cases and serious complications including obstruction and dense adhesions to the intra-abdominal mesh in four and a mesh-related abscess in one case.

Conclusion: This study highlights a dual problem – failure of a carefully sutured mesh to maintain an occlusive position, and complications of the mesh itself. The poor results obtained with this technique together with the disappointing results of other methods confirms that parastomal hernia presents a continuing challenge.

Study of quality of life in relation with the health after the surgery of the endoscopic inguinal hernia vs conventional

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Aim: The analysis of the results about the surgery treatment of the hernias can not be limited to the determination of the morbidity and recidiva, but it must be included in the study of the quality parameters. Descriptive valoration of the life quality after the surgery of the endoscopic inguinal hernia vs conventional, taking use of two questionnaires of a health status measures and the analysis of the association between the declarate life quality and the different variables pre and perioperatories.

Materials and methods: Prospective and randomized study performed on 59 patients (53 men and six women) with a previous informed consent, in 31 was practised an endoscopic preperitoneal hernia-plasty (TEP) and in 28 an open hernia-plasty type Nyhus (O). All patients were operated on under regional anaesthesia. They registered filiation facts, type of work, level of studies, type of hernia, associated illness, etc. Also were filled up the pain levels and the mobility of two questionnaires of generic perceived health (SF-36 Health Survey and the Nottingham Health Profile NHP) before to the intervention and in the seven and 30 days of the postoperatory.

Results: The 56 per cent of the 59 patients of the study were working before the intervention and the 32 per cent returned to work at 30 days of the intervention, not existing significative differences between both groups. The average score of the two questionnaires administered correspond to a moderate global affectation to the perceived health after the intervention. The pain level of the NHP in the seven and 30 days of the intervention, with regard to the postoperatory, was bigger in the O (16 vs 4·6; P=0·08) and (15·4 vs 3·9; P=0·02) than in the TEP (12·6 vs 8·5; P=0·486) and (9·5 vs 8·9; P=0·9). The satisfaction level of the patients with both surgery techniques was 96 per cent.

Conclusions: The reduction of the secondary functional discapacity to the pain observed in the endoscopic group allowed the reduction of the hospital stay, the transitory work incapacity and will improve the quality of life of the sick people operated of inguineal hernia.

Randomized controlled double-blind trial to prove the effects of postoperatively applied local anaesthesia in reducing pain level in patients after tension-free inguinal hernia repair

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A prospective randomized double-blind study was performed on patients undergoing Tension Free Hernia Repair using the techniques of Lichtenstein. On the first postoperative day the patients were given either local anaesthesia (LA-group) or isotonic sodium solution (NaCl-group) through a drainage tube which was placed intraoperatively into the inguinal canal. The aim of the study was to evaluate a possible relief from pain in patients due to the postoperative use of local anaesthesia after Tension Free Hernia Repair.

Two groups, namely LA and NaCl, each consisting of 30 patients undewent Tension Free Hernia Repair. During the operation, which was performed under local anaesthesia, a drainage tube was placed beneath the aponeurotic layer of the external oblique muscle. On the first postoperative day the patients of the LA-group received local anaesthesia and the patients of the NaCl-group received isotonic sodium solution through the drainage tube, which was subsequently removed from the wound. The application of the solutions was performed in a double blind technique.

During a period of 6 days, from the operation day onwards, the perceived level of pain was measured with the help of a Visual Analogue Scale (VAS). All patients were mobilized early, latest 4 hours after the operation.

Comparing the pain sensation levels (VAS) between the two groups it could be observed that the patients of the LA-group experienced no significant advantage throughout the observation period.

This clinical trial demonstrated that the application of local anaesthesia 24 hours after Tension Free Hernia Repair does not significantly reduce the perceived level of pain in patients. This kind of analgesia is therefore not recommended as a postoperative analgesia after hernia repair.

Mesh prosthesis inguinal hernia repair: review of 492 consecutive cases

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Background: The use of a prosthetic material in repair of inguinal hernias is becoming common because it is less invasive and technically simpler and faster than traditional techniques and with a lower recurrence rate reported.

Material and methods: Our experience with 492 adult inguinal hernia mesh prosthesis repairs from 1993 to 1995 is reported. Lichtenstein's tension-free hernioplasty, and Trabucco's and Gilbert's sutureless techniques were used according to the personal choice of each surgeon of the team. The mesh was polypropylene, in a minority of cases PTFE Anaesthesia was general in 380 cases, spinal in 60 and local in 52. Two hundred and forty-eight patients have been followed up from 6 months to 2 years.

Results: Sixteen complications occurred for a rate of 6·4 per cent. There were five recurrences (2 per cent), three wound infections (1·2 per cent), four oedemas of external genitalia (1·60 per cent), four hematomas and ilioinguinal neuralgias (1·60 per cent). In two cases it was necessary to remove the mesh. There was no mortality and no venous thrombosis.

Conclusions: For the good results obtained, particularly the low recurrence rate compared with the traditional repair, we advocate the more extensive use of the prosthesis tension-free technique as the first choice procedure for all adult hernias, not only for recurrent, but also for primary or first-time hernias. The cost of the material is counterbalanced by lower need of postoperative analgesia, shorter hospitalization and a lower risk of recurrence. Nevertheless, we think that Bassini repair, nowadays the most widely used method, should be still included in the repertory of any general surgeon as the basic operative technique for inguinal hernia.

Pancreatogastrotomy after duodenopancreatectomy: analysis of 160 consecutive patients

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Introduction: During the past 5 years, several papers exhibited a postoperative mortality of less than 8 per cent after pancreaticoduodenectomy, and no mortality in some skilled teams. Controversies exist about the advantages of the pancreato-gastrostomy over the classical pancreato-jejunostomy. In the present study the results of the pancreato-gastrostomy in 160 consecutive patients are assessed, and commented with special references to a collective review of the literature.
Patients and methods: From 1987 to 1996 all the patients referred to our department for a pancreatico-duodenal resection, underwent a pancreato-gastrostomy whatever age and status of the patient, the indication of the pancreatic resection and the texture of the remnant pancreas. There were 109 (68 per cent) males and 51 females (32 per cent). Mean age was 59±10 years (range 22 to 82), 27 patients were older than 70.
Results: In hospital mortality was 3 per cent (*n*=5). Overall morbidity was 30 per cent (*n*=49). Overall rate of pancreatic fistula was 2·5 per cent (*n*=4). Re-operation was required in 19 patients (12 per cent). Bleeding of the pancreatic section represented the main cause of re-operation complication (*n*=7). Delayed gastric emptying underwent in 22 per cent of patients (*n*=36). Mean hospital stay was 22 days ± 9, but was significantly longer in cases of delayed gastric emptying or pancreatic fistula.
Conclusion: Pancreatogastric anastomosis was feasible in all cases and yielded to a low mortality and morbidity rate. Others comparative prospective studies are mandatory to clearly define its place in the armamenterium of surgeons dealing with pancreatic resection. These studies should be reserved for expert centres with large volume of pancreatic resection, experienced surgeons, and a basic mortality and pancreatic fistula rate of less than 5 per cent.

Pancreatico-jejunostomy for chronic pancreatitis

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Drainage of the pancreatic duct in the treatment of chronic pancreatitis (CP) can be performed either surgically or endoscopically. Endoscopic drainage has been claimed to be associated with less morbidity and mortality, however long term results seem to be controversial.
Patients and methods: To assess our results of surgical treatment, 30 patients (M:F=26:4, mean age 42·6±13 years, range 25–80) who had undergone pancreatico-jejunostomy for CP were analysed. Aetiology of CP was alcohol abuse in 25 patients, biliary obstruction in three and idiopathic in two patients. Indication for surgery was persisting, severe abdominal pain. Surgical procedures included cysto-jejuno- or cysto-gastrostomy (10×), pancreatico-duodenectomy (4×), pancreatico-jejunostomy (12×), distal pancreatectomy (2×), subtotal pancreatectomy (2×).
Results: Postoperative complications occurred in four patients; mortality was 0 (the mean period of follow-up is 30 months, range 6–70 months). Immediate pain relief was seen in 96·6 per cent; only one patient complained of significant residual pain after surgery and could not discontinue his analgesic medication. Long term pain relief was complete in 47 per cent of the patients and partial in 50 per cent, in half of whom the pain related to recurrent alcohol intake. Ten patients had an abnormal OGTT of which seven needed increased doses of insulin after surgery. Nutritional status remained poor in six patients who did not gain weight after surgery. One patient needed a revision of the pancreatico-jejunostomy.
Conclusion: Pancreatico-jejunostomy is an efficient procedure resulting in pain relief in 93 per cent of the patients with total rehabilitation in 72 per cent. In patients with CP selected for a drainage procedure, surgery is a safe and reliable therapy.

Immediate and long term results of pancreaticojejunostomy in chronic pancreatitis

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Aim: To evaluate the results of pancreatico-jejunostomy in the treatment of chronic pancreatitis.
Patients and methods: From 1978 to 1995, 120 patients (105 males, 15 females with a mean age of 46 years) underwent pancreatico-jejunostomy (PJ) for chronic pancreatitis (CP). Alcohol abuse was presented in 105 cases (87·5 per cent). PJ was the unique procedure in 67 cases; it was associated with a biliary or a duodenal diversion in 38 cases and five cases respectively. In 10 cases, three diversions were performed.
Results: Postoperative mortality was 1·6 per cent (*n*=2), postoperative morbidity was 10 per cent (*n*=12). Mean hospital stay was 16 days (8–25 days). Fifteen patients (13 per cent) required a second operation some years subsequent to the PJ due to the progress of the CP or alcohol abuse. In the late postoperative course 22 deaths occurred (18 per cent), eight of them were directly related to alcohol abuse. Mean follow-up was seven years. Good and medium results for pain were achieved in 92 per cent of patients, but the progression of exocrine or endocrine pancreatic insufficiency indicated that wirsung decompression was insufficient to stop the progressive sclerosis.
Conclusions: Our results suggested that PJ was the best surgical procedure in CP treatment, when the wirsung was dilated.

Double loop reconstruction in Roux-en-Y mode after pancreaticoduodenectomy: a way to decrease postoperative morbidity and mortality?

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Aim: Pancreaticoduodenectomy (PD) continues to be associated with a high postoperative morbidity despite the improvement in operative technique and perioperative care. The use of two separate intestinal loops for anastomosis of the biliary tract and pancreas may decrease the rate of postoperative morbidity. The purpose of this study was to determine the incidence and cause of significant complications, and death following PD and compare double loop reconstruction after PD with standard reconstruction.
Patients and method: Between 1991 and 1997, 23 patients underwent PD because of periampullary neoplasm in 19 patients, recurrence after the local resection (ampullectomy) for ampullary tumour in one patient, duodenal invasion of the right colon tumour in two patients and choledochal cyst in one patient. Of the 23 patients, 14 were male and nine were female, with a median age of 52 years (range 26–72 years). Of the 23 patients, 10 (43 per cent) had undergone previous laparotomy in various centres: right hemicolectomy for colon carcinoma in two, cholecystectomy and T-tube drainage in two, cholecystectomy and choledochoduodenostomy in two, ampullectomy for ampullary tumour in one, gastrotomy for biopsy and gastrojejunostomy in one, gastronomy for biopsy in one and exploratory laparotomy for choledochal cyst in one patient. Ten patients underwent standard Whipple's procedure, nine pylorus-preserving PD and four PD with double loop reconstruction in Roux-en-Y mode (one jejunal segment for reconstruction of biliary tract and duodenal anastomoses and another for reconstruction of pancreatic anastomosis). The pancreatic remnant was anastomosed to the jejunum with an intussuspecting end-to-end anastomosis in all patients. All procedures were performed by the same surgeon.
Results: One or more significant complications prolonging hospitalization or resulting in a postoperative death occurred in six (26 per cent) patients. A single complication, pancreatic leak, developed in two patients, while four patients had two or more complications (leak in pancreatic and biliary tract anastomoses and pancreatic necrosis in one patient, leak in all anastomoses in one patient, leak in pancreatic anastomosis and intra-abdominal haemorrhage in two patients). Anastomotic leak from the pan-

creaticojejunostomy was the cause of all other complications and significantly associated with postoperative morbidity in this series (P=0·002). Three patients underwent reoperation for complications (re-pancreaticojejunostomy and control of bleeding in two patients and re-pancreaticojejunostomy in one patient). Of these patients only one survived reoperation. The overall postoperative mortality in this series was 17 per cent (n=4). There was no complication and mortality in the patient who underwent double loop reconstruction in Roux-en-Y mode. Although the patients with double loop reconstruction had shortened hospitalization (14 days vs 20 days) and operative time (380 minutes vs 420 minutes), this difference did not reach statistical significance (P<0·05).
Conclusion: The results of this study have shown that postoperative morbidity and mortality was significantly associated with the dehiscence of the pancreaticojejunostomy anastomosis. Two separate intestinal loops for anastomosis of the biliary tract and pancreas could be used to decrease the rate of postoperative morbidity and mortality.

Single layer continuous sutured anastomosis technique in pancreato-biliary surgery

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Authors evaluated the safety of anastomosis performed with absorbable single layer continuous sutures in various surgical procedures in pancreatic and biliary surgery. In the prospective, non-randomized study 156 anastomoses were performed on 92 patients during the last two years. All procedures – including Whipple and pylorus-preserving pancreatoduodenectomy (PPPD), duodenum-preserving resection, longitudinal pancreatico-jejunostomy or -gastrostomy and biliodigestive anastomoses in case of irresectable pancreatic tumour or chronic pancreatitis – were carried out by the same surgeon. In all cases they used size 3/0 or 4/0 polyglecaprone 25 (Monocryl, Johnson and Johnson) or glycomer 631 (Biosyn, USSC) with single layer, running stitches.

The types of anastomoses: 26 longitudinal pancreatic anastomoses (17 Wirsungo-gastrostomy and nine Wirsungo-jejunostomy), 43 biliodigestive anastomoses (mainly choledocho-jejunostomy sec Roux) and 87 small intestine anastomoses (duodeno-jejunostomy end to end in the case of PPPD or jejuno-jejunostomy in the case of Roux-Y loop). Two minor biliary leakages were detected after bilio-digestive anastomoses. There were no leakage after longitudinal pancreatic anastomoses or duodeno-jejunostomy. No patient required reoperation for anastomosis related complication. Three patients died – but the complications were not connected with the suture technique.

The authors' opinion is that the described method is safe, easy to carry out, physiological and least harmful to the blood supply, so they recommend its use in pancreato-biliary surgery.

Failure of CT scan and ERCP in detecting proximal pancreatic and peri-pancreatic diseases

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Aim: To analyse the findings of CT scan and ERCP for small volume proximal pancreatic and peri-pancreatic disease.
Materials and methods: Twenty-eight proximal pancreatic resections have been carried out in the last 3 years. Twenty-seven patients have undergone high resolution conventional or spiral CT scan (5 mm and 4 mm collimation respectively). All resected specimens underwent serial sectioning to demonstrate small volume disease. Twenty-five pateints also had ERCP.
Results: Final diagnoses of these 28 patients comprise 10 benign lesions (three acute pancreatitis, two chronic pancreatitis, one sclerosing cholangitis, two mucinous cystadenoma, one adenomatous hyperplasia and one villous adenoma) and 18 malignant lesions (10 adenocarcinoma of head of pancreas, three cholangiocarcinoma, three ampullary carcinoma, one carcinoid and one carcinoma of gallbladder). CT scan identified 13 lesions of which four suspected benign lesions were confirmed histologically. Of nine suspected malignant lesions only five were confirmed histologically and four were benign. In nine patients CT scan failed to identify a lesion but subsequent histology confirmed seven malignant and two benign lesions. All the five equivocal lesions on CT scan were malignant. ERCP cannulation failed in two cases (carcinoid and cyst adenoma), one ruptured pancreatic duct diagnosed secondary to acute pancreatitis. In three cases ERCP was normal, histology revealed two adenocarcinoma head of pancreas and one chronic pancreatitis. ERCP suspected 18 malignant lesions, histology confirmed 13, but five were benign.
Conclusion: Where clinical suspicion remains, a pancreatic resection should be seriously considered, even in the face of negative or equivocal CT scan or suspicious ERCP.

Restorative proctectomy with coloanal J pouch for obstructed defecation – an early appraisal

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Aim: Impaired rectal evacuation remains a challenging clinical problem. A variety of surgical options such as correction of anatomical abnormalities (if present), ACE (antegrade colonic enema) procedures and colostomy have been tried, but have met with limited success. The present study evaluates the use of proctectomy with coloanal pouch anastomosis in patients with intractable difficulties in rectal evacuation.
Materials and methods: Nine patients (eight females; 1 male; median age 44 years, range 34 to 63 years) underwent proctectomy with coloanal pouch anastomosis. Preoperative evacuation proctography was undertaken in all patients and findings included rectorectal intussusception (n=5), rectocele (n=6) and pelvic floor descent (n=4). In seven of the nine patients, delayed or incomplete evacuation was observed radiologically. Endoanal ultrasonography revealed co-existent sphincter defects in three patients and four patients had abnormal rectal compliance on anorectal physiology.
Results: Restorative proctectomy with stapled coloanal **J** pouch anastomosis was performed in all patients. A temporary loop ileostomy was constructed in two of these and both have been reversed. There were no perioperative complications. At a medium follow-up of 6 months (range 1·5 to 12 months), all patients report a subjective improvement in rectal emptying. The median frequency of bowel evacuation is three (range two to five) times daily. All remain continent of flatus and faeces.
Conclusions: The results of this preliminary study indicate that restorative proctectomy with coloanal pouch may have a role in the surgical management of patients with intractable difficulties in rectal evacuation.

Distal intramural spread of rectal carcinomas

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The aim of the study is to examine distal rectal spread of rectal cancer and to determine the optimal distal margin of resection after sphincter saving resection (SSR).

At the Institute of Clinica Chirurgica of the University of Trieste 438 operations for rectal cancer were performed, 314 of which were for curative purposes.

The choice of the type of operation was related only to the location of the tumour; neither the stage, nor other risk factors were considered. To this purpose 220 SSR were performed. In 50 selected of these cases, distal intramural spread was detected. Surgical specimens were pinned under tension onto a wooden board and, below the distal edge of the tumour, a number of full thickness sections of 1 cm were performed.

In two cases a tumoral distal spread at 1 cm was observed, whilst an involvement beyond 2 cm was never demonstrated. The two cases with distal spread at 1 cm were advanced cancer with a full thickness infiltration, without nodal involvement; these patients were classified as G_2, one was aneuploidy and both had a high proliferation index.

The authors conclude that in the surgical treatment of rectal cancer, SSR is justified, provided a distal margin of 2 cm is respected. Even in advanced cancers a distal spread of over 2 cm has never been observed.

Laparoscopic-assisted colonic resection for diverticulitis: prospective study in 50 patients

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Aim: To evaluate the feasibility, the safety and the results of laparoscopic-assisted colonic resection for diverticulitis.
Materials and methods: The surgical technique was a laparoscopically-assisted procedure: under laparoscopy, total mobilization of the left colon and vascular ligation were performed and then via a small abdominal incision (8 cm length), division of the colon, removal of the specimen and hand-sewn anastomosis. This approach was prospectively used in 50 consecutive patients (23 males, 27 females with a mean age of 62 years). The delay of surgery after the last acute attack of diverticulitis varied from one to four months.
Results: The surgical goal was achieved in 46 cases. In four cases (8 per cent), the laparoscopic dissection was unsuccessful and the procedure was converted via a large midline incision. The mean operative time was 195 minutes (150–280). There was no mortality and the morbidity rate was 14 per cent. No complication was directly related to the laparoscopic technique. The mean return of regular bowel habits was 3·2 days and the median postoperative stay was 10 days (6–22).
Conclusion: These preliminary results suggest that the laparoscopic-assisted sigmoidectomy can be used safely for the surgical treatment of diverticular disease. This approach seems to be technically easier and cheaper than the totally laparoscopic approach but reduces the expected advantages of minimal invasive surgery.

First 100 operations with MASA-2 anastomotic device in low anterior resection

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The authors present their experiences in the first 100 operations practised for rectal cancer localized in the middle and lower third of the rectum with an anastomotic device developed by one of them. There were 61 men and 39 women between 36 and 78 years. Fifty-eight patients received preoperative radiotherapy (30 Gy), at 40 patients they applied total mesorectal excision.
Results: Spontaneous discharge of the anastomotic device was after nine days on average (range 6–14 days). Anastomotic dehiscence developed in 20 patients (20 per cent). Four patients died within 30 days. For all patients with total mesorectal excision the authors recommend a covering loop colostomy.
Conclusions: 1) The anastomotic apparatus is suitable to practise an air and watertight low colorectal anastomosis where this was not guaranteed by manual techniques. 2) After spontaneous discharge of the device foreign material does not remain in the tissues. 3) Its application necessitates a special technique. 4) Owing to the equal circular compression around the whole rim of the gut, bleeding does not occur. 5) In cases of total mesorectal excision a loop colostomy is recommended. 6) It is less expensive.

Relevant points to consider for selection of patients with peritoneal carcinomatosis for cytoreductive surgery and IP chemotherapy

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Aim: In an attempt to improve knowledge of the methodologies and relevant points to consider in order to the selection of patients with peritoneal carcinomatosis from colon and rectal cancer for treatment with cytoreductive surgery and intraperitoneal chemotherapy.
Material and methods: A group of 86 patients with biopsy proven peritoneal carcinomatosis from colon and rectal cancer, treated with cytoreductive surgery and early postoperative intraperitoneal chemotherapy using Mitomicin C and 5-Fluorouracil was retrospectively studied. An analysis of clinical features of these patients was performed using survival as an end point for evaluation of prognosis.
Results: These data suggest that the clinical features to be used to select patients for cytoreduction were completeness of resection at the time of the cytoreductive surgery, as 64 per cent of patients were alive at 3 years if no visible tumour remained or implants were less than 0·25 cm in diameter, but none was alive when tumour implants persisted greater than 0·25 cm in diameter (P=0·04). A peritoneal cancer index (PCI) was calculated by combining the lesion size and the abdominopelvic regions

affected, providing a score for composite involvement of the disease that was in close relation with survival. Patients with 12 or less PCI showed a statistically significantly better prognosis than those who had a higher score (P=0·066).

Conclusions: A peritoneal curative intent should be considered in patients with limited distribution and volume of peritoneal carcinomatosis defined by the Peritoneal Cancer Index (PCI).

Comparison of large bowel anastomoses using biofragmentable anastomotic ring and single layer continuous suture: a prospective randomized study

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Background: Nowadays the biofragmentable anastomotic ring is widely accepted in colonic surgery, but there is less experience with using one layer continuous suture.

Aim: This prospective, randomized study was to compare the efficacy of the sutured anastomosis with the biofragmentable anastomotic ring (BAR) in colonic surgery.

Patients and methods: All patients undergoing elective colon resection between 1 April 1995 and 31 December 1997 were included in the study. Only if the ratio of bowel lumens at the site of anastomosis was larger than 1·7:1 the patient was excluded and in this case end to side anastomosis was performed. In the study group all anastomoses were constructed end to end.

Results: From 69 patients with end to end colonic anastomoses 32 were randomized in the suture group (12 ileocolic and 20 colocolic anastomoses). The BAR group included 14 patients with ileocolic and 23 patients with colocolic anastomoses (n=37). The mean age of patients with BAR anastomosis was higher (66 years) than those with sutured anastomosis (62 years). There was no significant difference between the two groups considering body mass index, ASA score, the ratio of benign and malignant diseases and TNM staging. In the suture group one patient (3 per cent) with multiple liver metastases died in the early postoperative period. There was no operative mortality in the BAR group. Two patients (5 per cent) with anastomotic leakage after BAR anastomosis were treated with Hartmann's procedure. There were not clinical signs of leakage in the suture group. From the five (14 per cent) surgical complications in the BAR group three required re-operation. Only a few postoperative complications, two wound sepsis, a deep venous thrombosis and a cardiac arrhythmia were observed in the suture group (12·5 per cent). Duration of BAR anastomoses was shorter than duration of sutured one (15 vs 18 minutes), but the overall duration of operation and hospital stay were nearly the same in the two groups.

Conclusions: These results suggest that the single layer continuous suture is as safe as the BAR for colonic anastomoses. The higher percentage of re-operation in the BAR group was due to the inadequate purse-string sutures in the first five cases and the higher age of patients. The BAR anastomoses cost 15 times more than their sutured counterparts.

Loop ileostomy is a method for temporary faecal diversion

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Aims: Loop ileostomy is a feasible method for temporary diversion of faecal stream in colorectal surgery. The technical steps of the operation and the aetiology of complications are discussed along with the characteristic features of the postoperative period.

Materials and methods: During the period from November 1992 to March 1996, 34 loop ileostomies were created and restored usually after 14 weeks. The loop ileostomy protected the suture lines of 15 ileoanal anastomoses, of 18 colorectal or coloanal anastomoses and of one perineal construction. Loop ileostomy was supported by a rod inserted beneath the intestine, the afferent limb was averted and the mucocutaneous line was created. Complete diversion of the faecal stream was achieved in all cases. High-volume faecal output necessitated the administration of Imodium in 26 per cent of the cases. However, permanent parenteral fluid and electrolyte replacement was unnecessary. Stoma necrosis, bleeding, prolapse or retraction did not occur. Stomas were closed intraperitoneally in all cases but one. Two asymptomatic hernias were observed at closure. The continuity of the intestine was restored by the inversion of the previously opened and averted intestine in 13 cases, or by small resection in 21 cases (14 end-to-end, seven side-to-side anastomoses).

Results: The average length of the postoperative hospital stay after closure was nine days. Passage of the intestinal contents started 3 days following the closure in patients with ileoanal anastomosis and 2 days in patients with colorectal anastomosis. Clinical signs of prolonged postoperative ileus were observed in five cases, re-operation was necessary in two cases due to mechanical bowel obstruction. Wound infection developed in three cases.

Conclusion: Loop ileostomy is a simple and effective method for the temporary diversion of faecal stream with low morbidity. The creation and closure of loop ileostomies was not associated with any mortality.

Functional results of sphincter-saving surgery for distal rectal cancer

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Sphincter saving resection with low colorectal or coloanal anastomosis, as the alternative to abdomino-perineal excision should provide not only safe oncological outcome, but also good functional results.

The aim of this study was to assess the functional results of low rectal resections. The records of 27 patients who underwent rectal resection with low colorectal or coloanal anastomosis (and who had their diverting colostomies closed) from 1 January 1994 to 31 December 1996 were reviewed. There were 17 men and 10 women, with the mean age of 61·8 (38–78) years. The mean distance of the tumour from the anal verge was 6·9 (4–10) cm. The surgical technique was anterior resection (AR) in 16 cases and abdomino-transsphincteric resection (ATSR) in 11 cases. The anastomosis was made by hand sutures in four cases, by EEA stapler in six cases and with double stapling technique in 17 cases. A diverting colostomy was performed in 22 cases. Anastomotic leakage occurred in five cases (18·1 per cent).

The mean time elapsed from the closure of diverting colostomy was 19·7 (3–46) months. The continence was assessed by personal interview and classified according to Kirwan–Fazio. We found: 13 patients with normal continence, eight patients with the continence of gases impaired, four patients with occasional, minor soiling and two patients with frequent soiling. The mean stool frequency was 2·7 (1–12) per day. The stool frequency has decreased and the continence score has improved in time. No major soiling was found after six months from the stoma closure. No significant difference related to the type of resection (AR or ATSR) or to the suture technique was found. All the patients are satisfied with their sphincter function and prefer it to the colostomy.

These data confirm that sphincter-saving procedures for distal rectal cancer provide good functional results.

The phantom rectum: fact or fiction?

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Aim: To investigate the prevalence of phantom perineal sensation following rectal amputation.

Methods: An audit database and stoma care records identified 60 patients who had regular stoma therapy following abdomino-perineal resection and pan-proctocolectomy. A postal questionnaire was sent to all patients and replies were cross-referenced with hospital records for accuracy.

Results: Forty-three patients responded (72 per cent). Median age was 67 (range 20 to 87) years. Median follow-up was 48 (range 3–369) months. Thirty-one patients (72 per cent) experienced phantom perineal sensation. This was described as the need to pass faeces rectally in 21 patients (68 per cent), need to pass wind in 15 (48 per cent), a dull ache in 12 (39 per cent) and nine patients (29 per cent) experienced shooting pains. The duration of symptoms was usually one to two minutes but ranged from a few seconds up to two hours. In 30 of the 31 symptomatic patients (97 per cent), the symptom remained the same or became less severe with time, and completely disappeared in 25 per cent (eight patients) within 6 months. Nine patients (29 per cent) described the symptoms as distressing. Four patients (13 per cent) experienced symptoms related to stoma function. Four patients experienced relief by pressure on the buttocks, two with analgesia and one patient by sitting on a toilet seat. Six patients (19 per cent) sought medical advice because of this symptom: relief was obtained by reassurance in three cases, simple analgesics in two cases; and one was found to have tumour recurrence. No patient had a further surgical procedure. The majority of patients expressed a desire to have been warned to expect these symptoms.

Conclusions: Phantom perineal sensation is a real phenomenon, but does not appear to be a long-term clinical problem. Pre-operative patient counselling may relieve distress, although in all cases tumour recurrence should be excluded.

Has the surgical technique of choice in complicated acute diverticulitis changed? A prospective non-randomized study of 185 patients

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Aim: To analyse 265 patients diagnosed with acute diverticulitis over a period of 20 years, comparing the indications and surgical techniques performed in two consecutive 10-year periods, together with the morbidity and mortality rates of the series.

Material and methods: A prospective study was made of 185 cases (group B) over a period of 10 years (1987–1996), who were compared with a retrospective series of 80 patients (group A) (1977–1986). 53·5 per cent of the patients required surgery whereas the remaining 46·5 per cent were treated conservatively. The indications for surgery were faecal peritonitis (16 cases), purulent peritonitis (39 cases), pelvic abscesses (40 cases), pericolic abscesses (nine cases), intestinal obstruction (15 cases), recurrent diverticulitis (19 cases) and colovesical fistula (four cases). The most commonly employed surgical techniques were resection and closure of the stump according to Hartmann (82 cases), without significant differences between the two periods, and resection with primary anastomosis (40 cases), with significant differences between the periods (14·8 per cent vs 36·3 per cent in group B) ($P<0·05$). 42·7 per cent of the patients undergoing the Hartmann operation had reconstruction of digestive continuity in a second intervention.

Results: There were postoperative complications in 40·1 per cent of the patients without statistically significant differences between the two periods. The postoperative mortality rate was 9·1 per cent, with statistically significant differences (14·8 per cent vs 5·7 per cent in group B) ($P<0·05$).

Conclusions: In our experience, the Hartmann operation is an efficient surgical procedure, especially if there is purulent or faecal contamination of the abdominal cavity, but we advocate resection with primary anastomosis following intraoperative lavage of the colon in the early stages of peritoneal contamination due to the minimum morbidity and zero mortality rates.

Surface hydrophobicity human colonic mucosa: role of epidermal growth factor

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The colonic mucosal barrier is a complex physico-chemical structure that separates the internal 'mileu' from a polluted luminal environment. Animal studies have shown that the barrier includes a strong hydrophobic surface to prevent the flux of water-soluble toxins in the epithelium.

Our aim was to explore the hydrophobic properties of the human colonic mucosa. Colonic specimens were obtained at surgery from patients undergoing colectomy for neoplasm (n=38) or diverticulitis (n=5). Preparation for surgery was similar in all patients and included antibiotic therapy (erithromycin-neomycin) and gut lavage with PEG solution. Specimens from normally appearing colon were washed in saline, and the mucosa was dissected and sectioned in 3 × 2 cm samples. In total, surface hydrophobicity was measured in 83 separate colonic samples by the contact angle that conform a 5 µL drop of saline deposited on the mucosal surface using a special goniometer. Large contact angles are read on hydrophobic surfaces whereas small angles are formed on hydrophillic surfaces. In four patients, nine samples were assessed straightforward after surgery, and 14 samples were incubated for 60 minutes with or without epidermal growth factor (EGF, 2 µg/mL) Krebs–Ringer (pH 7·4) at 37°C prior to hydrophobicity measurement. Phospholipid content was measured in homogenates of 25 samples.

Results: Mucosal hydrophobicity was similar in right colon (40±1·0°), left colon (42±0·9°) or rectum (42±0·8°). Likewise, no difference was found in phospholipid content between right colon (202±1·2 mol/g), left colon (199±17) or rectum (226±23). Incubation of mucosal samples increased surface hydrophobicity (baseline: 39±0·4°; post-incubation: 44±1·8°, P 0·05), suggesting active release of surfactant. Exposure to EGF significantly increased hydrophobicity (49±1·6°) as compared to incubation without EGF (44±1·8, P 0·05).

Conclusion: The human colonic mucosa exhibits a hydrophobic surface, which can be regulated by endogenous growth factors such as EGF.

Cost-benefit problems in colorectal surgery in Hungary

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The costs of surgical procedures are increasing all over the world, because of new technical instruments and high salaries of surgeons and their assistants. That is a great problem in Hungarian hospitals, because the relatively low Hungarian GDP allows less and less budget for the hospital costs. The prices of instruments are well determined, but the prices of 1 hour's work in the operating room is not fixed even today in Hungary.

Clinical study was performed between 1st January 1990 and 31st December 1997. The goal of this study was to compare the perioperative data of patients with elective colorectal resections because of malignancies. The operator and the preoperative preparation of patients were the same. The patients were divided into two groups. One group had operations with colon-anastomosis, the other with rectal anastomosis.

Data of 203 patients (105 female and 98 male) were analysed. One hundred and sixteen anastomoses were performed on the colon (68 of them were hand sewn and 48 were made by linear staplers). The rectal operations were divided into three groups. There was a group for patients with hand sewn anastomoses, a group for patients with anastomoses sutured by one EEA circular stapler, and there was one group for patients operated on with double-stapler technique. The groups were comparable. Distribution of sex, mean age and mean body weights were similar.

The mortality and complication rates were similar in the groups of patients with colon anastomoses. But the operative time was significantly shorter in the group of anastomoses made by linear staplers. Unfortunately, the cost of operation was higher because of prices of linear staplers. The author could not determine how much cost was spared by the shorter operating time.

The mortality rates were similar in the groups of patients with rectal anatomoses. The complication rate was the lowest and the operating time was the shortest in the double stapling group. Unfortunately, the cost of operation was the highest in that group because of the prices of two staplers. The authors could not determine how much cost was spared by the shorter time and the lowest complication rate.

The role of immunological factors in wound infections (a prospective clinical study)

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Wound infections are observed in 1·5–4 per cent of clean and 28–40 per cent of contaminated wounds. One of the intervening factors in the development of wound infections is the present immunological status of the patient.

Aim: To investigate the relationship between the immunological status of the patients and wound infections. The effect of different treatment modalities on the immunological status of the patients and the state of immunological parameters as being criteria in the efficiency of the treatment have also been investigated.

Materials and methods: Wounds were grouped into three as clean, clean-contaminated and dirty wounds. Each group consisted of 15 patients. The patients who had received radiotherapy or chemotherapy and who were immune compromised were excluded from the study. T-lymphocyte (CD3+), B-lymphocyte (CD19+) and total lymphocyte (CD45+) counts, and IgG, IgM and IgA levels were measured at the beginning of treatment, at the fifth and tenth days. The immunological changes were compared within and between the groups with ANOVA test.

Results: The levels of CD3+, CD19+, CD45+, IgM, IgA were not different in all the groups, while in the dirty group, IgG levels were lower than the other groups at the beginning of the treatment ($P<0\cdot05$). At the fifth and tenth days of the treatment, IgG levels increased and CD19+ level decreased in the dirty group ($P>0\cdot05$). Two patients in the contaminated group died during the treatment. These two patients had a progressive decrease in the levels of IgG and CD19+ ($P>0\cdot05$). There was no change in the levels of CD3+, CD19+, CD45+, IgG, IgM and IgA in the clean and clean-contaminated groups at the fifth and tenth days of the treatment.

Conclusions: The possibility of development of wound infection is higher in the patients having lower IgG at the beginning of treatment and in the patients having progressive decrease of CD19+ levels during the treatment.

The value of augmentin prophylaxis in colorectal surgery: a double blind randomized prospective study

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Authors report a double-blind randomized prospective study to evaluate the efficacy of Augmentin in the pretreatment of elective colorectal operations. In this comparative (Augmentin vs Zinacef-Metronidazole) randomized, one day prophylaxis trial 90 patients were involved. In group A the randomly selected 40 patients were pretreated with Augmentin (3·6 g/day) and 50 patients in group B with Zinacef-Metronidazole combination (4·5 g/day Zinacef and 1·5 g/day Klion). The factors potentially influencing the results – age, stage of the disease, type of surgery, risk factors, accompanying diseases – were similar in the two groups. The efficacy of antibiotic prophylaxis has been compared based on time of postoperative hospitalization, wound healing, rate of septic complications, etc. The average number of postoperative hospitalization days showed no significant difference: 14·9 days in group A, and 12·3 days in group B. The mortality rate of the 90 patients was 2·2 per cent. Both patients died from group A, so the rate of mortality in group A has been 5 per cent, and 0 per cent in group B. The rate of septic complications was 27·5 per cent in group A while the one in group B has been only 20 per cent. Our results show that the efficacy of Zinacef-Metronidazole combination seems to be superior related to the solitary Augmentin pretreatment in colorectal surgery.

Bileodigestive anastomosis or external drainage of the biliary tree in benign diseases of the gallbladder

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Patients with diseases of the gallbladder tend to increase annually judging from our data and from reports in literature.

In the first surgical department of the Medical University Pleven during the period 1990–1997, 1134 patients were operated for benign diseases of the biliary tree, gallbladder and pancreas either on emergency basis or planned. We report 324 patients in whom we performed cholecystectomy with temporary or permanent drainage of the bile.

The aim of the study was:

1. Definition of indications for performing one or another operation.
2. Comparison of results from treatment modalities – during the course of the study the criteria for choledochotomy was defined – stones in the ducts choledochus, expanded ducts choledochus, purulent cholangitis, biliary fistulas, mechanical jaundice.

Choledocho-duodenal anastomosis and choledochotomy with external drainage have their respective indications. We recommend choledocho-duodenal anastomosis.

Vancomycin prophylaxis for MRSA wound infections

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Introduction: The incidence of methicillin-resistant *Staphlococcus aureus* (MRSA) infections is increasing. This is of particular importance in vascular surgery where graft infection is associated with a significant mortality. We have therefore reviewed the incidence of MRSA wound infections following the contribution of three doses of 500 mg vancomycin i.v. as part of the routine prophylaxis for major vascular procedures on our unit.

Method: Patients were included from January 1996 to May 1997. Inter-hospital transfers and patients previously known to harbour MRSA were screened on admission to the unit. Only patients without known MRSA infection or colonization and having major vascular procedures from our vascular ward or the ITU are included. Postoperatively wound swabs were taken if there was clinical suspicion of infection or if MRSA was isolated from another site.

Results: Before the introduction of the vancomycin there were six MRSA wound infections in 122 patients (4·92 per cent), after there were 16 infections in 344 patients (4·65 per cent). The number of MRSA-positive patients admitted to the ward per month was constant throughout the period studied (median 1, range 0–3). Furthermore, the number of operations and discharges per month were also constant (median 47, range 30–55 and median 44, range 31–62 respectively). The total number of MRSA wound infections from all procedures performed was 1·6 per month before May 1996 and 1·58 thereafter (i.e. 4·02 per cent and 3·58 per cent respectively).

Conclusion: The policy of vancomycin prophylaxis has had no significant effect on MRSA wound infection in the period studied.

Peritoneal and biliary penetration of selected antibiotics in surgical inflammatory conditions

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The study was undertaken to estimate the peritoneal and biliary penetration of ceftazidime, cefoperazone, amikacin and netilmicin – drugs useful in the treatment of intra-abdominal sepsis. The trial included patients given an antibiotic in the perioperative period either as a prophylaxis or a treatment of infection.

Samples of serum, peritoneum and bile were obtained on operation after the patient was administered the first dose of an antibiotic preoperatively. Concentrations of drugs were determined by bioassay in an agar well diffusion method. Concentration of an antibiotic was assessed with standard strains: *E. coli* ATCC 25922 for cefalosporins and *B. subtilis* ATCC 6933 for aminoglycosides. Time-course drugs concentrations was calculated with the least-squares regression analysis.

One hour after 2 g of cefoperazone administration in 28 patients its peritoneal concentration was within therapeutic range (~30 μg/g) and was maintained on more or less same level for next 4–5 hours, with little patient-to-patient deviation.

Maximum ceftazidime concentrations (17 patients), exceeding 40 μg/g, were observed also one hour post injection, but major differences between patients were noted.

Amikacin (13 patients) reached maximum level in the peritoneum (~4 μg/g) 3 hours after administration followed by its slow decrease, parallel to that in the serum. Netilmycin concentration (in 30 patients) exceeded and was maintained longer than that of amikacin, reached maximum values one hour post administration and was kept stable for next three hours. Seven hours following administration it was still well above 3 μg/g.

Biliary concentration of cefoperazone was assessed in two groups of patients: with and without jaundice. Maximum concentration of the drug in patients without evidence of jaundice (20 patients) after administration of 1 g exceeded 500 μg/ml and was maintained for 3 hours and followed by a slow decrease – seven hours after administration it was about 10 per cent lower than maximum value.

Ceftazidime (seven patients) reached maximum level (45 μg/ml) in 1 hour and was followed by a slow elimination phase parallel to the serum drug kinetics.

Both aminoglycosides reach maximum biliary levels (~4 μg/ml) after 3 hours, but netilmycine (20 patients) maintains its concentration for next 4 hours, while amikacine (15 patients) level falls proportionally to its blood concentration and after 7 hours is only 1 g/ml.

Clostridium difficile infections in our practice of colorectal surgery

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Clostridium difficile (CD) is an anaerobic bacterium which may cause severe entero-colitis. Its relatively high incidence in colorectal surgery may be due to the use of antibiotics in the bowel preparation and in the postoperative period. The three clinical forms of CD infection, in order of increasing severity, are: 1) antibiotic associated diarrhoea (AAD); 2) antibiotic associated colitis (AAC); and 3) antibiotic associated pseudomembranous colitis (AAPMC).

The records of 1215 patients who underwent colorectal operations from 1988 to 1997 in our department have been reviewed. The diagnosis of CD infection was based on bacterial culture and on a specific cytotoxin assay of the stool.

The different protocols of preoperative antibiotic prophylaxis (Cefuroxmin + Clindamycin, Cefotaxim + Metronidasol, Sulbactam + Ampicillin, Amoxicillin + Calvulanic ac. + Metronidazol) did not show significant difference in the rate of CD infections.

After having reported elsewhere four severe cases of AAPCM in the first five year period (1988–1992), in the second period (1993–1997) we have made changes in the bowel preparation protocols, the suspicion of CD infection was questioned earlier and the specific laboratory tests were used more often in CD infection suspect cases.

Period	No. of patients	Negative test	AAD	AAC	AAPCM
1988–1992	604	33 (5·5%)	59 (9·8%)	13 (2·1%)	4 (0·7%)
1993–1997	611	57 (9·3%)	30 (4·9%)	13 (2·1%)	2 (0·3%)

Metronidazole was the therapy of first choice in test positive cases. If the clinical signs did not show improvement after 24 hours, Vancomycin therapy was started.

Zinc as an inhibitor of apoptotic DNA fragmentation in isolated perfused rat liver

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Zinc is an important intracellular ion with many important biological effects, including preventing DNA fragmentation due to apoptotic cell death. We have successfully achieved blockage of DNA fragmentation in apoptosis induced by bloodless perfusion in IPRL.

Our model of apoptosis involves perfusion of rat liver with modified Krebs solution containing glucose and hydroxyethyl starch at 37°C, either after flushing with cold UW and 24 hour storage at 4°C in the same solution, or flushing only without preservation. Perfusion flow rate was 2·5–3 ml/gm/min. Liver specimens were collected at 0, 1, 3, 5 hours and freeze clamped in liquid N_2. DNA was isolated using standard phenol chloroform extraction and electrophoresed on 1·5 per cent w/v agarose gel, stained with ethidium bromide 40 µg/L (w/v) and visualized by UV light.

A single band of genomic DNA close to the loading point was found in all livers perfused with zinc 25 µM + zinc ionophore 4 µM rich solution (n=8) between 0–5 hours perfusion. In contrast, perfusion of livers by calcium-channel blocking agents verapamil (50 mg/kg) or chlorpromazine (25 mg/kg) containing solution were without suppression of apoptosis. The DNA ladder was comprised of frequent multiples of approximately 200 base pairs. In addition, livers cold preserved in zinc and ionophore containing UW solution and perfused with Krebs solution only had shown no suppression of DNA degradation.

In summary, DNA laddering pattern characteristics of apoptosis disappeared consistently in rat livers perfused with zinc sulfate treated solution. Addition of calcium antagonist was without effect. Further study to investigate the mechanism of DNA fragmentation blockage by zinc is required.

Isolated perfused rat liver: a model of induction of apoptosis by bloodless perfusion

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Apoptosis or programmed cell death is an active mechanism, with well-described morphological and biochemical components and is a known physiological process initiated by a variety of stimuli including renal ischaemia. We here investigated apoptosis as indicated by characteristic DNA degradation or laddering in isolated perfused rat livers (IPRL).

Rat livers were flushed with cold solution and perfused with modified Krebs' solution containing glucose and hydroxyethyl starch (COLLOID) at 37°C and oxygenated with 95 per cent O_2 and 5 per cent CO_2. Perfusion flow rate was 2·5–3 ml/gm/min. Liver specimens collected at 0, 1, 2, 3 hours and freeze clamped in liquid N_2. DNA was isolated using standard phenol chloroform extraction and electrophoresed on 1·5 per cent w/v agarose gel, gel stained with ethidium bromide 40 µg/L (w/v) and visualized by UV light.

A single band of genomic DNA close to the loading point was found in all livers (n=4) between 0–2 hours perfusion. In contrast, we found DNA laddering indicative of apoptosis at 3 hours perfusion in all livers. The ladder was comprised of frequent multiples of approximately DNA 200 base pairs. Livers (n=4) flushed with warm solution (37°C) to avoid temperature shock also showed laddering at 3 hours. Changing the perfusion system from non-recirculating modes to recirculating did not prevent DNA laddering after 3 hours perfusion. Addition of thiol-saving agents reduced glutathione (500 mg/L) and N-acetyl cysteine (300 mg/L) were also without effect. Recent histological examination has confirmed the appearance of apoptotic bodies in the tissues of IPRL.

In summary, IPRL under these conditions consistently produces DNA laddering after 3 hours and may be a model to investigate pharmacological interventions in apoptosis.

Significance of biochemical parameters in early diagnosis of strangulated bowel obstruction (experimental study)

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Aim: Although the diagnosis of simple mechanical bowel obstruction is easy and prognosis is good, the surgical timing is quite difficult in strangulated cases where a delay in diagnosis may effect the morbidity and mortality adversely. The value of biochemical parameters in early diagnosis of strangulated bowel obstructions in rats with simple and strangulated bowel obstruction was investigated in this study.

Materials and methods: Fifty male Wistar Albino rats were used. Rats were separated into two groups of 20 rats and one group of 10 rats. In the first group (control group-CG) laparotomy only was applied and 1 ml of blood sample was withdrawn. In the second (simple obstruction group-OG) and third (strangulated obstruction group-SOG) groups simple or strangulated obstruction 5 cm proximal to ceacum was established. Two and 12 hours postoperatively in the first 10 rats, and 4 and 24 hours postoperatively in the other 10 rats 0·5 ml of blood samples were withdrawn. Analyses of lactic acid (LA), lactic dehydrogenase (LDH), creatine phosphokinase (CPK) and amylase were done.

Results: Serum LA, LDH, CPK and amylase values were significantly higher (P<0·05) in OG and SOG at 2 hours postoperatively and during 24 hours than those of CG. But only LA and amylase values were significantly higher (P<0·05) in SOG at 2 hours postoperatively and during 24 hours than those of OG.

Conclusions: It is concluded that although the serum LA and amylase values are not specific for bowel obstructions, it may be valuable in early diagnosis of strangulated bowel obstructions if their levels are found to be elevated in the early stage of strangulation.

The effects of dimethylsulfoxide in liver ischemia

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Aim: We determined the biochemical and cellular changes arising in liver during the ischaemia period of Pringle manoeuvre and then did research into the effects of DMSO, non-enzymatic oxygen free radical scavenger and Na^+-K^+-ATPase inhibitor.

Material and methods: Twenty-four albino rabbits of New Zealand type weighing 2350–2550 g were used. The experiment consisted of two groups, called study and control. In the study group, Pringle manoeuvre was applied for 60 minutes, but no application was made in the control group. The study and control groups were divided into two groups of six rabbits as those given and not given DMSO.

Results: In the ischemia group given DMSO the decrease in the blood glucose values turned into increase after the 30th minute. There was a decrease of 29 per cent in glycogen values after 60 minutes ischaemia in the ischaemia group not given DMSO, this decrease was 20 per cent in the ischaemia group given DMSO. The increase in LDH and AST levels was not statistically meaningful in the ischaemia group given DMSO (P>0·05). It was shown that DMSO did not have a preventive effect on the increase in ALT values occurring in the liver ischaemia (P<0·05). The decrease in ATP level was found only meaningful in the group given DMSO (P<0·05). It was observed that DMSO caused MDA levels increasing after the liver ischaemia to decrease meaningfully (P<0·05). In the ischaemia group after DMSO was given, the increases in SOD levels in the erythrocyte were not meaningful (P>0·05) and GSH-rd levels went down quite meaningfully (P<0·01). DMSO causes a decrease after 30th minute in GSH-px values going up in the liver ischaemia (P<0·01).

Conclusion: It was observed that DMSO had a positive effect in the experimental liver ischaemia on the values of blood glycose, liver glycogen, blood ATP, AST, LDH, blood and tissue MDA, GSH-px, GSH-rd and SOD in accord with the purpose of the experiment. However, no positive effect on ALP and ALT values was observed. DMSO may be used in order to reduce the negative effect of ischaemia in the liver tissue.

The effect of aminoguanidine and L-Arginine on neutrophil chemotaxis and bacterial translocation in rats after endotoxin challenge

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Aim: Inhibition of neutrophil chemotaxis and increased bacterial translocation are the two important factors associated with high mortality in sepsis. In this study, we aimed to investigate the effect of inhibition of nitric oxide synthase (NOS) with aminoguanidine (AG), which is relatively more specific for inducible NOS, and administration of a nitric oxide precursor, L-Arginine, on neutrophil chemotaxis and bacterial translocation in a rat sepsis model.
Material and methods: Sixty male Wistar Albino rats were randomly assigned into six groups: (1) group 1, normal saline solution (NSS, 0·6 ml/kg/h for 4 hours); (2) group 2, lipopolysaccharide (LPS, 10 mg/kg intraperitoneally 2 hours before the experiment); (3) group 3, NSS and aminoguanidine (AG, 5 mg/kg bolus and 5 mg/kg/h infusion for 4 hours); (4) group 4, LPS and AG; (5) group 5, NSS and L-Arginine (L-Arg, 100 mg/kg/h infusion for 4 hours); (6) group 6, LPS and L-Arg. Additionally, rats in all groups received 15 ml of sodium caseinate intraperitoneally, 12 hours before the experiment for the study of chemotaxis. Animals underwent laparotomy at 4 hours of experiment. Peritoneal fluid was taken for the study of neutrophil chemotactic index (ratio of chemoattractant-induced neutrophil migration in micrometers to random migration); tissue samples of liver, spleen, mesenteric lymph nodes, ileum and caecum were taken for histological examination and bacterial translocation studies. For statistical analyses, Duncan multiple range test, Friedman test and χ^2-square tests were used.
Results: LPS given intraperitoneally was found to inhibit neutrophil chemotaxis and increase bacterial translocation statistically in this model. L-Arg and AG administration significantly increased chemotactic index and decreased translocation after endotoxin challenge (Table 1). Despite the decrease in bacterial translocation and bacterial population level in cecum after AG administration in septic rats, these figures were significantly high when compared with normal rats. On the other hand, L-Arg decreased translocation and bacterial population in cecum to the levels found in normal rats and preserved mucosal integrity in small intestine in septic rats.

Groups	Chemotactic index (mean±s.d.)	Translocation incidence to mesenteric lymph nodes	Bacterial population in cecum ($\times10^6$/gram-tissue)	Intestinal mucosal damage score
NSS	1·60 (±0·23)	0/10†	0·4±1·8Ê	9§
LPS	1·26 (±0·10)	9/10	5·5±4·2	21
NSS+AG	1·04 (±0·04)	–	–	–
LPS+AG	1·80 (±0·16)*	4/10†	2·3±2·4†	16
NSS+L-Arg	1·68 (±0·03)	–	–	–
LPS+L-Arg	1·79 (±0·01)*	0/10†	0·5±1·1†	11§

NSS, normal saline solution; LPS, lipopolysaccharide; AG, aminoguanidine; L-Arg, L-Arginine; *$P<0{\cdot}05$ LPS+L-Arg and LPS+AG vs NSS and LPS; †$P<0{\cdot}05$ LPS+AG vs LPS; ‡$P<0{\cdot}05$ NSS vs LPS+AG; §$P<0{\cdot}05$ NSS and LPS+L-Arg vs LPS.

Conclusion: The results of this study have shown that administration of L-Arginine and aminoguanidine induced neutrophil chemotaxis and increased chemotactic index after endotoxin challenge in rats. Additionally, L-Arginine preserved intestinal mucosal integrity which, in turn, inhibited bacterial translocation in this sepsis model.

The role of oxygen free radicals and nitric oxide in haemorrhagic shock and tissue injury due to reinfusion

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Aim: Haemorrhagic shock is a hypovolaemic condition that leads to haemodynamic decompensation associated with ischaemic metabolic insufficiency caused by inadequate tissue perfusion, altered cell membrane permeability and subsequent cellular dysfunction. Haemorrhagic shock followed by resuscitation is a generalized whole-body ischaemia-reperfusion insult. The purpose of the present study was to evaluate the role of oxygen free radicals and nitric oxide (NO) in physiological alterations and multiple organ damage caused by haemorrhagic shock and reinfusion.
Materials and methods: Twenty-six mongrel type dogs were used in this study. The dogs were let to bleed till the arterial blood pressure fell to 35 mmHg and they were kept in shock for 1 hour. Three randomized groups were formed. The control group ($n=10$) received 10 ml 0·9 per cent sodium chloride, the NO group ($n=8$) received 250 mg/kg L-arginine and L-NAME group ($n=8$) received 25 mg/kg L-NAME intravenously in the 55th minute of the haemorrhagic shock. After the shock period, the shed blood was returned. Blood and tissue samples were taken before experiment, after 1 hour of shock and 2 hours after the reinfusion. The biochemical results, enzyme, nitrite-nitrate levels were compared with ANOVA test and χ^2-square test was used for the evaluation of histopathological results.
Results: The mean arterial pressure fell after the infusion of L-arginin, whereas L-NAME infusion resulted in significant increase of blood pressure. The infusion of L-arginin after haemorrhagic shock was found to increase myocardical injury and renal dysfunction developing secondary to shock ($P<0{\cdot}05$). L-arginin was found to decrease hepotocyte and intestinal injury secondary to shock and reinfusion. L-arginin caused significant decrease of endogenous free radical scavengers within erythrocytes and liver tissue ($P<0{\cdot}05$).
Conclusions: NO infusion in haemorrhagic shock caused renal and myocardial injury by increasing hypoperfusion and had protective effect on liver and intestinal tissue, probably by adjusting the microcirculation. Whereas inhibition of NO synthesis aggravated reinfusion injury.

Prevention of peritoneal adhesions by streptokinase, phosphotidylcholine and diclofenac-sodium in New Zealand white rabbits

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The formation of peritoneal adhesions after operations remains a serious problem and is probably the most common cause of the intestinal obstruction. In this study we investigated the effect of three different agents in the prevention of peritoneal adhesions induced by caecal abrasions in New Zealand white rabbits. Group I ($n=16$) acted as controls. Group II ($n=16$) received 100 000 IU/kg streptokinase; group III ($n=16$) received 3 mg/kg diclofenac-sodium and group IV ($n=16$) received a total dose of 50 mg phosphotidylcholine given intraperitoneally in 20 ml saline just before the closure of abdominal cavity. Fourteen days later all animals were killed, abdominal cavity was inspected and assessed by two 'blind' surgeons who did not attend the initial operation using a new wide paramedian incision. All adhesions were graded from 0 to 4 according to Mazuji[1] and scored from 0 (grade 0, 1) to 1 (grade 2–3–4) according to Elkins[2]. Thirteen (81 per cent) animals in group I, 11 (69 per cent) in group II, 11 (69 per cent) in group III and six (37 per cent) in group IV had adhesions. The difference between control and phosphotidylcholine group was significant ($P<0{\cdot}03$), whereas no difference was observed among the other groups. The adhesions were significantly low graded in group IV than all other groups ($P<0{\cdot}005$). The scoring of the adhesions also revealed that the phosphotidylcholine group had only 2 (12·5 per cent) significant adhesions, which was 8 (50 per cent) in diclofenac-sodium group, 11 (69 per cent) in streptokinase group and 13 (81 per cent) in controls ($P<0·0006$ for group 4–1, $P<0·005$ for group 4–2, $P<0·05$ for group 4–3). This study suggests that the phosphotidylcholine is better agent than all others in reducing the incidence and severity of peritoneal adhesion formation induced by caecal abrasions.

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The role of neurogenic inflammation in the process of healing of experimental colon anastomosis

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Aim: The tissue perfusion enhancing neuropeptides which act in opposition to the sympathetic vasoconstrictor tone, seem to play an important role in the regulation of tissue microcirculation adjusted to the actual metabolism under different physiological and pathological circumstances The aim of this study was to explore the effects of inhibition of neurogenic inflammation, i.e. alteration in local neuropeptide activities on the healing process of experimental colon anastomosis
Materials and methods: Sigmoid colon anastomosis was performed in infant and adult male Wistar rats, which had been previously treated by Capsaicin In the second postoperative day the anastomosis bursting pressure (ABP) and the blood vessel permeability changes were registered by Evans Blue Extravasation Technique.
Results: In the adult Capsaicin-treated group the ABP value was 50±5 per cent more than the control group On the other hand, in the infant group the ABP was significantly higher than that of the control group (90±8 mmHg $n=11$ vs 54±5 mmHg $n=27$ $P<0·01$) In the adult treated group the Evans Blue extravasation was numerically lower than the control group
Conclusion: The inhibition or the damage to the Capsaicin sensitive C and A-delta nociceptive afferent fibres decreases the inflammation reaction in the area of the anastomosis and enhances its healing Our previous results suggest that the inhibition of the neurogenic inflammation may contribute to the increase of the number of the successful anastomoses

The influence of pneumoperitoneum on peritoneal implantation and growth of spleen cell suspension in an experimental model

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Aims: An investigation of the effect of laparoscopy and CO_2 pneumoperitoneum on the pattern of tumour-like spleen tissue suspension implantation and growth in the intra- and extraperitoneal space was carried out
Materials and methods: Ten animal models weighing 15–20 kg were used, five for laparoscopy with pneumoperitoneum, three for gasless laparoscopy and two for laparotomy. Animals for gasless laparoscopy and laparotomy consisted the control group In all cases partial resection of the spleen of the animal model was carried out through a laparotomy and a 2 ml of homogenous spleen suspension was prepared in each case The spleen suspension was then placed in the subhepatic region In the laparoscopy group the laparotomy was closed and four 10 mm trocars were placed in the upper and lower abdomen and CO_2 was insufflated and desufflated in 10-minute intervals at each port site for one hour, followed by the removal of the trocars. In the control group of laparotomy the laparotomy was simply closed, and in the group of the gasless laparoscopy the abdomen was closed over a laparolift for also one hour, and then the lift removed and the incision was closed.
Results: All animals survived. Four weeks following the experiments all animals underwent re-laparoscopy to detect spleen tissue implantation and growth. In the group of the pneumoperitoneum excessive implantation was observed around the intra- and extraperitoneal port sites, and spleen tissue seeding was found in all the peritoneal surfaces of the abdominal cavity In the control groups only scattered spleen tissue implantation was detected intraperitoneally. Histological results confirmed these findings.
Conclusions: The results of this study support the issue of the role of pneumoperitoneum in the cellular aerolization, the implantation and the growth of spleen tissue intraperitoneally and in the extraperitoneal space when compared to laparotomy and gasless laparoscopy, supporting the postulate that early port side wound metastases and early carcinosis and tumour spread may be more likely following laparoscopic oncological surgery in humans when CO_2 insufflation and desufflation (Chimney effect) is used

Renal autotransplantation in extracorporeal renal surgery for severe renal vascular hypertension

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Introduction: Experience in renal transplantation has resulted in the development of extracorporeal surgical techniques to treat various vascular and urologic conditions of the kidney. Among the vascular problems which can be successfully managed by extracorporeal renal surgery and autotransplantation, are renal artery stenosis resulting from atheroma, fibro-muscular disease, segmental artery aneurysms.
Method: We have used the technique of extracorporeal hypothermic benchwork surgery with autotransplantation with renal vascular problems and severe hypertension requiring 3–4 drugs in three patients aged 16–30 years. Two patients had obstructing aneurysm of branches of renal artery and one had bilateral renal artery stenosis with severe myocardial dysfunction. All patients were evaluated according to a specific protocol, including renal function studies, isotope renograms, IVP, renal angiography and cardiac function studies. The kidney is removed after mobilization of the ureter and dividing both renal artery and vein. It is then immediately cooled by perfusion with Eurocollin solution and it is placed in a kidney dish outside the wound while appropriate bench surgery is carried out with magnifying loops. The kidney is then autotransplanted lower down in the abdomen on the common iliac artery and vein. The patient is placed on subcutaneous heparin for several days and then on oral aspirin.
Results: All patients fully recovered with normalization of their blood pressure and improvement in renal function with no anti-hypertensive medication. Renal isotope scan showed marked improvement in renal flow and function. In the patient with bilateral renal artery stenosis, post surgical cardiac study showed reversal of cardiomegaly with left ventricular diameter falling from 7 to 5 cm and the ejection fraction rising from 20 to 40 per cent within four months.
Conclusion: Extracorporeal renal surgery with autotransplantation is a very effective and successful method of renocascular hypertension of all causes and it should be more widely practised.

Are modular bifurcate aortic stent grafts (ASG) succeeding?

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Aims: To assess the mid-term results of the Vanguard ASG for the treatment of abdominal aortic aneurysms (AAA).
Methods: Over a 28 month period, 371 AAAs have been assessed using CT scans. Calibrating angiography was performed on 129, of which 64 were repaired using a Vanguard ASG. Patients have been followed up clinically and with regular contrast enhanced CT scans. Morbidity and mortality are assessed with particular reference to limb patency and perigraft flow (endoleak).
Results: All deployments were successful. Exclusion of the aneurysm sac was achieved in 55 patients (86 per cent). There were three deaths (perioperative mortality 4·7 per cent) but no major complications. Of four proximal endoleaks: one sealed spontaneously, one persists and two patients died following attempted open repair. Another patient died from an MI on day three. Of five endoleaks, three sealed spontaneously and two required further endovascular intervention. Six grafts have suffered unilateral limb occlusion and CT has identified three late distal endoleaks, each requiring endovascular repair. Three further patients have died (>30 days, two unrelated, one graft infection).
Conclusion: Mid-term results confirm that modular bifurcate ASGs are suitable for the treatment of selected AAAs. The development of late endoleaks is a cause for concern and continued follow-up is required.

Laparoscopic aorto-iliac reconstructive surgery: a prospective study

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Most recently there have been several reports dealing with laparoscopically assisted aorto-iliac surgery. So far there has been no controlled study evaluating the possible benefits for the patient with aorto-iliac occlusive disease when this minimal invasive technique is used. It was the purpose of our study to assess the possible benefits of the minimal invasive technique and the consequences on the clinical course.
Material and methods: In a prospective controlled study lasting 11 months 24 patients with aorto-iliac occlusive disease were included into the study protocol. Exclusion criteria were aneurysmal disease, morbid obesity with a body mass index >30 or the necesssity for suprarenal aortic clamping. The control group consisted of 12 patients in whom a transperitoneal median laparotomy was performed for aorto-bifemoral bypass grafting. In the study group there were 12 patients who were operated using a transperitoneal minilaparotomy (5 cm) and a laparoscopically assisted approach. The aorta was dissected up to the origin of the renal arteries using the minilaparotomy as an access and with the help of standard surgical instruments. The proximal anastomoses after crossclamping of the aorta was sutured with conventional surgical instruments. End points of the prospective study were postoperative hospital stay, analgesic requirement, time point of postoperation oral feeding and ICU stay as well as ventilatory support. In addition, pre- and postoperative pulmonary function tests (FEV1, VC) were performed on the fourth postoperative day (statistical analysis by t-test, SPSS statistical package).
Results: There were no major complications in either group. Total operative time (225 ± 25 minutes) was significantly longer ($P<0{\cdot}02$) in the study group. There was a higher degree of pulmonary impairment in the conventional group compared to the laparoscopic group of patients. A regular diet could be resumed significantly earlier and patients were discharged sooner in the minimal invasive group. Patency rates did not differ in either group. Patients required significantly less analgesics when the laparoscopic technique was used.
Conclusion: We can infer from our data that using a video assisted technique the operative trauma as assessed by the postoperative course of patients is reduced. They benefit from less pulmonary impairment compared to a conventional procedure. This leads to a faster recovery and a shortened postoperative hospital stay. Therefore, this technique can offer a minimal-invasive alternative to endovascular procedures yet with well established long term results using standard vascular surgical techniques. The laparoscopic technique as such still requires significant improvements before a widespread use can be recommended.

Screening of Abdominal Aortic Aneurysms (AAA): a pragmatic approach

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Aim: To evaluate the feasibility of a selective screening programme for AAA in men at the age of 65 within an urban setting and assess its impact on the expected increase in workload for the local hospital(s).
Materials and methods: 4823 men aged 65 were invited for ultrasound examination of the abdominal aorta between January 1993 and April 1997 as part of a General Practice based aneurysm screening programme covering two districts with a general hospital each. All examinations were carried out by senior radiographers using a portable B mode grey scale machine and a 3·5 MHz curvi-linear array probe. Patients with a maximum aortic diameter of over 3 cm were annually recalled, those with over 4 cm were referred to hospital for an outpatients appointment. Those with AAA greater than 5 cm were considered for surgery.

Results: 3497 (72·5 per cent) took part in the study, 1206 (25 per cent) did not attend and 120 (2·5 per cent) were excluded by their General Practitioners (GPs) on medical grounds. 3130 (89·5 per cent) had an aortic diameter equal or less than 2·5 cm and 196 (5·6 per cent) between 2·6 and 3·0 cm. 171 (4·9 per cent) had aortic diameters greater than 3 cm, 29 of whom had AAA greater than 5 cm with a mean diameter of 6·0 cm (range 5·1–9·0 cm). Of 127 with an initial diameter of 3·1–4·0 cm (mean progression in size of 2·3 mm/year) 22 enlarged to >4 cm and 3 to >5 cm. Of 24 with an initial diameter of 4·1–5·0 cm six enlarged to >5 cm. Sixty-nine (2 per cent) patients were referred to hospital. Eighteen underwent surgery, three are on the waiting list (one for endovascular repair) and one died (from rupture) while awaiting his operation. Five patients refused their operations and two failed to attend the clinic (all >5 cm) but remain well to date. No patient died following surgery.

Conclusions: Screening for AAAs in men aged 65 within an urban setting is feasible and well received by patients and GPs. Screening does not lead to a huge increase in terms of out-patient appointments and operations for AAA.

Graft dilatation following abdominal aortic aneurysm resection and grafting

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Dilatation of aortic prostheses following abdominal aneurysm surgery has been documented with both knitted and woven dacron grafts.

Aim: To review the experience in a single institution with both types of grafts, and to evaluate both rate and degree of dilatation, and association of dilatation with graft related complications.

Materials and methods: Between January 1987 and December 1992, elective repair of abdominal aortic aneurysm was undertaken in 219 patients. Of these patients, 146 had at least one follow-up ultrasound scan to evaluate their graft. These patients were analysed with respect to age, sex, size of initial aneurysm, type of graft used, time of follow-up and diameter of graft at follow-up scan. Any complications referable to the graft or recurrent disease was also documented at this time.

Results: A total of 216 scans were available for analysis. There were 123 male patients and 23 female patients in the group. The mean age was 72 years, and the mean preoperative aneurysm size was 5·8 cm. Thirty-four patients had a woven dacron graft inserted, while 112 were grafted with a knitted dacron prosthesis. Mean percentage increase in size for woven dacron was 17·3 per cent, while that for knitted dacron was 38·9 per cent (P<0·0001). Further analysis of the scans showed that the majority of dilatation occurred early, and the grafts were then relatively stable. No specific complications related to graft or anastamotic dilatation were noted.

Conclusions: Dilatation following implantation is a well known phenomenon affecting dacron, particularly in a knitted configuration. Some authors have suggested that graft dilatation is either an inherent failure mode of the material, or a precursor of more significant complications. This study contradicts this view, and dilatation was not associated with any adverse outcome. However, graft complications are known to be related to the weight of graft inserted, particularly in knitted grafts, and there is some question as to the dimensional stability in vivo of ultralightweight grafts. This raises concerns as to the behaviour of grafts inserted during endoluminal repairs and the possibility of late dilatation.

The endothelial response in thoracoabdominal aneurysm repairs

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Introduction: Reperfusion injury following major aneurysm repair is associated with postoperative complications including renal failure and adult respiratory distress syndrome and the endothelium is an integral part of their pathophysiology. Thoracoabdominal aneurysm repairs necessitate visceral reperfusion and have a high incidence of multi-organ failure. We investigated the enothelial response to thoracoabdominal aneurysm repair and its relationship to complications.

Methods: Plasma was collected from 16 patients undergoing thoracoabdominal aneurysm repair at incision, clamp placement, clamp removal, 30 minutes, 120 minutes and 24 hours. Soluble Intercellula Adhesion Molecule-1 (sICAM) was assayed in all patients by an ELIS technique and endothelin-1 (ET-1) was assayed in 12. These result were grouped by patient outcome. All results are expressed as median with 95 per cent confidence intervals (C.I.) and analysed with non-parametric tests.

Results: Serum concentrations of sICAM shows a significant decreas at 30 minutes 158 ng/ml (95 per cent C.I. 125–182 ng/ml) from incisio 240 ng/ml (95 per cent C.I. 201–304 ng/ml) P<0·01. At 24 hours thos patients that went on to develop complications had significantl increased their levels of sICAM; 366 ng/ml (95 per cent C.I 259–473 ng/ml) P<0·02, those who did not develop complications ha raised levels of sICAM that did not reach significance 312 ng/ml (95 pe cent C.I. 267– 357 ng/ml) P=0·06. ET-1 levels were significantl increased at two hours from baseline levels of <0·1 pmol/ (0–0·247 pmol/L) to 0·62 pmol/L (0·3–1·01 pmol/L) P<0·01. The rise di not correlate with outcome.

Conclusion: During aneurysm surgery the endothelial function i changed. The degree of endothelial damage may predispose the patient t serious postoperative complications.

Three years experience with endovascular treatment of aortic aneurysms

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Background: Three years after introduction of endovascular treatment aortic aneurysms there is still controversy, first of the high costs an second of the unknown durability of the graft.

Methods: From October 1994 until October 1997 a total of 42 aneurys were treated at our institution by endovascular prostheses, 38 abdomin aortic aneurysms (AAA) and four thoracic aortic aneurysms (TAA). Fi AAA were repaired by tube endovascular graft (Mialhe Stento Vanguard), in 33 AAA a bifurcated endovascular graft (Mialhe Stento Vanguard, Talent) was inserted. The procedure was performed in gener (n=9), peridual (n=12), and local (n=17) anaesthesia. Indications for TA endovascular treatment (what about the indications for AAA treatment were traumatic aortic ruptures (n=2), aneurysm with aortobronchial fistu (n=1), and aortobronchial fistula (n=1) 20 years after correction of aort coarctation.

Results: In AAA no conversion to open surgical treatment was nece sary. Mean hospital stay was five days. There were two proximal ar seven distal leakages as primary complications. Five leakages we treated by placing a second endovascular graft. One patient died on d four at home because of myocardial infarction. Late events were tw thrombotic graft occlusions, two secondary leakages, three graft disl cations and a few peripheral thromboembolic incidents. Correction graft failures was performed either by endovascular or surgical re-inte vention.

Conclusion: Presently endovascular treatment of aortic aneurysms limited to about 25 per cent of patients with AAA or TAA by morph logical reasons and high costs for the implant. Because of complicatio within the learning curve and unknown long-term results we changed a more differentiated indication, when and how to apply endovascul techniques. Placement of endovascular stent grafts is an elegant meth for the treatment of aortic aneurysm especially in the elderly with po condition.

The early complications of femorofemoral cross over grafts following endovascular repair of abdominal aortic aneurysms

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Aim: Of the three main methods of endovascular repair (EVR) of abdominal aortic aneurysms (AAA), aorta aortic graft, bifurcated graft and aorta uni-iliac graft, the latter has the potential disadvantage of requiring an extra anatomic bypass, i.e. a femorofemoral cross over graft, in order to maintain contra lateral pelvic and limb perfusion. The aim of the study was to assess the complications associated with the femorofemoral cross over graft following aorta uni-iliac EVR of AAA.
Method: A retrospective review of the complications attributable to the femorofemoral cross over graft in 136 patients having EVR of AAA with an aorta uni-iliac device.
Results: Following a median follow-up of seven months (range 0–36 months), four patients had superficial wound infections requiring antibiotic treatment and two patients had graft infections. There were seven (5 per cent) groin haematomas, six in patients with Dacron grafts. There was only one graft thrombosis.
Conclusion: The femorofemoral cross over graft is a safe and durable component of EVR of AAA with an aorta uni-iliac device against which complications of the bifurcated devices should be compared.

Renal complications following endovascular repair of abdominal aortic aneurysms

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Introduction: Renal failure is a recognized complication of open repair of abdominal aortic aneurysms (AAA). Endovascular repair (EVR) of AAA has the potential to reduce this complication. The aim is to report the renal complications following EVR of AAA from a single centre.
Method: Prospective data collection on 164 pateints undergoing EVR of AAA. A history of renal failure and diabetes mellitus was recorded. Serum urea and creatinine levels were measured preoperatively and at regular intervals postoperatively. Renal impairment was defined as a serum creatinine greater than 130 μmoles/l.
Results: There was no significant difference in the pre and day one postoperative serum urea and creatinine levels. Fifteen patients had preoperative renal failure of which there have been seven deaths, four in the perioperative period. Of those patients with normal renal function preoperatively (n=149), four developed renal failure as part of multi system organ failure. Nine developed significant rises (20 per cent) in their creatine levels postoperatively when compared to preoperative values. Four of these nine patients have died, two in the perioperative period. There was no significant difference in the median contrast dose between those patients that did and did not have a deterioration in their renal function (300 mls vs 250 mls).
Conclusion: The incidence of renal impairment in those patients with originally normal renal function who go on to have EVR of AAA is 6 per cent. The mortality for those patients with known renal failure following EVR is high, 23 per cent in the perioperative period.

Adjuvant radiotherapy has no benefit after primary breast cancer treatment in selected postmenopausal patients

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The need of adjuvant radiotherapy after breast conserving surgery for localized breast cancer remains uncertain, especially in selected postmenopausal patients adjuvant irradiation may be spared.

We analysed 379 consecutive postmenopausal patients treated at our surgical department from 1983 to 1994. Surgical procedure was quadrantectomy and axillary dissection of level I+II in all patients. Only postmenopausal, lymph node negative patients with tumour diameter below 3 cm were included in this analysis. Half of the patients had adjuvant radiotherapy, the other part was not irradiated postoperatively. The influence of adjuvant radiotherapy on local recurrence free and overall survival was studied together with other prognostic factors both in univariate and multivariate manner.

Analysis of the tumour characteristics revealed 82 per cent of the patients having a tumour below 2 cm, 81 per cent had a well or moderate differentiated tumour and 78 per cent of the tumours were hormone receptor positive. After a median follow-up of five years adjuvant radiotherapy was unable to significantly reduce local recurrence free survival nor overall survival in this selected postmenopausal patients: 96 per cent of the patients without adjuvant radiotherapy and 98 per cent of the patients with radiotherapy were free of local recurrence (P=n.s.); overall survival was 89 per cent without radiotherapy vs 90 per cent in the irradiated group (P=n.s.). Multivariate analysis revealed none of the prognostic factors to be significant for local recurrence free survival; overall survival was found to be independently influenced by the receptor status (P=0·02).

In subgroup analysis of patients with hormone receptor positive tumours (250 patients) and those with adjuvant Tamoxifen therapy (181 patients) the local recurrence rate was under 3 per cent with or without adjuvant irradiation. In a prospective randomized trial of hormone receptor positive postmenopausal patients with different adjuvant hormone therapy after breast conservation we observed a local recurrence rate of 2 per cent with or without radiotherapy.

Therefore, we conclude that postmenopausal patients with positive tumour characteristics (Tu <3 cm, node negative, grading I or II, hormone receptor positive and adjuvant Tamoxifen therapy) have no benefit from adjuvant irradiation. A prospective randomized trial evaluating adjuvant radiotherapy in this patient group is currently in progress and we urgently await first results within the next years.

The specialist treatment of the axilla

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Aims: Previous reports have highlighted both the survival advantage to treatment by larger specialist units and also the poorer survival associated with inadequate axillary treatment. This report compares the adequacy of treatment of the axilla by specialists and non-specialist units and the outcome of this treatment.

Methods: All 7144 histologically confirmed invasive breast cancers in women under 75 diagnosed from 1980–1994 who lived in a defined geographical area (population 1·5 million) were identified. The original pathology reports and 1950 out of 2531 case records for the years 1986–1991 obtained.

Results: Specialists compared to non-specialists performed no axillary surgery in 448 (19 per cent) vs 1705 (36 per cent); inadequate sampling in 136 (6 per cent) vs 1013 (14 per cent); sampled 4–9 nodes in 927 (39 per cent) vs 2301 (32 per cent); and 10 + nodes in 828 (35 per cent) vs 1313 (18 per cent); χ^2=10007·70, 4DF, P<0·00000. From the case records: specialists compared to non-specialists performed no axillary treatment in eight (1 per cent) vs 148 (15 per cent); sampled less than four nodes only in 40 (5 per cent) vs 115 (11 per cent); sampled less than four nodes in 12 premenopausal women vs 124 (5 per cent vs 40 per cent of all premenopausal women treated); did not remove any axillary nodes in an axillary sample in six (15 per cent of women with an axillary sample peformed) vs 51 (44 per cent). Axillary recurrence rates were noted in 24 (3 per cent) vs 84 (8 per cent).

Conclusions: Specialists examine the axilla more frequently, more thoroughly, omit axillary surgery only in very selected cases, and consequently had a recurrence rate almost one third that of non-specialists. Inadequate axillary staging may have resulted in inadequate local control but also in the omission of chemotherapy in younger women.

Treatment of local recurrence following breast conserving procedure

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Local recurrence following breast conserving procedure can be treated successfully. The clinical significance of local recurrence, influencing factors and the principal of treatment is under evaluation. The incidence rate, integration of risk factors (age, tumour size, lymph node status, completeness of excision, multicentricity) strategy of therapy and histomorphological signs all prove to be predictable in retrospective studies.

Between 1976 and 1995 there were 1312 operations carried out for the treatment of breast cancer in the Department of Surgery of the Markusovszky County Hospital. Out of these operations 260 breast conserving procedures were carried out. Thirty-two patients died, 22 of which had recurrence. In 10 patients with local recurrence mastectomy was performed, in six further patients re-excision was carried out and there is no data available for the remaining patients.

It is important to take into account the size of the tumour, the axillary lymph node status and the patient's age. Retrospective histomorphological evaluation performed in 15 patients – an intraductal component within the tumour exceeding 25 per cent, grading, ductal carcinoma in situ in the surrounding and an abnormal mitosis activity index – revealed either in all but one positive. Tumour free survival rate was lower following breast conserving procedures as opposed to mastectomies, however following adequate treatment of local recurrences there were no differences in the overall survival rate.

In the authors opinion in case of a local relapse after breast conserving treatment mastectomy should be chosen as long as there are no exact qualitative and quantitative histomorphological results available concerning the original tumour and its recurrence and no algorithm for the tests of prognostic markers is known. Should any late recurrence occur – after five years – with a slowly growing tumour smaller than 2·0 cm, repeated wide local excision is acceptable. Regular follow-ups – including mammography and clinical examination – are important following breast conserving procedures to detect and treat any local recurrences.

Angiotensin receptor expression and axillary node metastases in breast cancer

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Angiotensin II (AII) is a biologically active peptide of the renin angiotensin system. Most of the known physiological actions of AII are mediated via its type I (ATI) receptor. AII regulates growth and development of tissues and thus may be an important factor in tumour progression. Using a specific monoclonal antibody we have previously shown ATI receptor expression in breast tissue.

Aims: The aim of this study was to extend our data and relate the expression of ATI receptor to disease progression and to determine quantitatively its relationship to factors known to have prognostic significance in breast cancer.
Methods: Formalin fixed paraffin embedded breast tissue sections from 151 women, aged between 22–84 years were examined by immunocytochemistry using the 6313G2 monoclonal antibody to the ATI receptor. A semi quantitative staining intensity index (SII) was used to determine the level of expression of the ATI receptor.
Results: Breast tissue from 151 patients were examined. breast cancers n=102 (67·5 per cent), benign breast disease n=47 (32·5 per cent). Of the breast cancers 37 (36·3 per cent) patients had metastatic axillary lymph node involvement. Semi quantitative analysis of the ATI receptor expression by SII revealed a range from 0·25–2·25. The mean score for receptor expression was higher in benign as compared to malignant breast tissue, but this difference did not reach significance (P<0·06). Analysis of the receptor expression in breast cancer showed no relationship with tumour grade but was shown to be significantly correlated with lymph node involvement (P<0·03).
Conclusions: The expression of ATI receptor appears to be higher in benign as compared to malignant breast tissue. Patients with axillary nodal involvement show a reduction in receptor expression compared to node negative patients, suggesting AII may be involved in breast cancer metastasis.

Outcome of inconclusive cytology in mammographically screen-detected breast lesions

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Aim: To correlate the cytological findings and radiological opinion with final histology of mammographically screen-detected breast lesions and to predict the likelihood of malignancy.
Materials and methods: Cytological and radiographic data were collected prospectively in 2137 women who had had fine needle aspiration (FNA) of mammographically suspicious breast lesion in a screening programme. These data were compared with the final histology of excised specimens.
Results: 192 (9 per cent) of the FNAs showed atypica (C_3) and 114 (5 per cent) high suspicion of malignancy (C_4). Of the C_3 lesions 88 (46 per cent) were benign and 104 (54 per cent) malignant (90 invasive and 14 in situ); and of the C_4 lesions 15 (13 per cent) were benign and 99 (81 per cent) malignant (85 invasive and 14 in situ); χ^2 32·8, P<0·001. Radiological opinion of the mammograms was graded R_1 (not malignant) or R_5 (malignant). When C_3 cytology and R_5 radiology were combined 56 of 65 (86 per cent) lesions were malignant; and when C_4 and R_5 were combined 52 of 53 (98 per cent) were malignant; χ^2, P<0·05.
Conclusion: FNA is widely used for exclusion or confirmation of malignancy in mammographically screen-detected breast lesions. When cytology is inconclusive the accurate prediction of malignancy can be improved by combination with radiological suspicion prior to definitive histological diagnosis.

Expression and clinical signification of lysozyme in male breast carcinoma

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Lysozyme is a major protein component of human milk. The object of this study was to evaluate the lysozyme tumoral expression and its clinical signification in 57 male patients diagnosed with breast carcinoma and without metastasis at the moment of diagnosis. Mean follow-up period was 41·3 months. Tumoral expression of lysozyme was evaluated by immunihistochemical methods, using antiserum against lysozyme and following the biotin-streptavidin method with the Supersentivie system (Biogenex, San Ramon, CA, USA).

A total of 35 tumours (61·4 per cent) stained negatively for lysozyme, one (1·75 per cent) carcinoma stained weakly positive, 14 (24 per cent) stained moderately positive, whereas the remaining 12 (21·05 per cent) tumours stained strongly positive for this enzyme. No significant correlation was found between lysozyme immunostaining and age of patients, tumour size, lymph node involvement, histologic grade or oestrogen receptor status. However, analysis of relapse-free survival (RFS) showed that high lysozyme values were significantly associated to shorter RFS periods (P<0·05). In addition, multivariate analysis according to Cox's regression model showed that tumoral lysozyme expression was an independent prognostic factor able to predict RFS (P<0·05).

These results led us to consider that lysozyme may represent a new prognostic factor able to identify subgroups of MBC patients with low or high risk for relapse and death.

Kidney tumours in children

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Aim: We assess 12-year experience of management of 81 children with kidney tumours.
Materials and methods: The patients' age ranged from 1 month to 14 years. The study population consisted of 39 boys and 42 girls. The benign neoformations were diagnosed in seven (8·6 per cent) cases. Seventy-four (91·4 per cent) patients had a malignant tumour. Right side localization of the tumour took place in 31 cases (38·3 per cent), left side – in 50 (61·7 per cent). Among the patients with malignant tumours nephroblastoma was diagnosed in all cases. The further management devised was taking into consideration general condition of the patients, the extent of tumour differentiation and process stage. Preoperative polychemotherapy were carried out. In all the cases operative treatment was used (transabdominal nephrectomy). Polychemotherapy, telegammatherapy as well as immunotherapy and phytotherapy were carried out postoperatively.
Results: Twenty patients (76·9 per cent) with I-II stage of the Wilms' tumour are living for 2–10 years. Among the patients with III-IV stage 16 children (33·3 per cent) are living. The others died against the background of an aggressive tumour and progression of the process. Only one patient with IV stage of the nephroblastoma are living. General mortality range was 55·56 per cent. Among benign neoformations (7 patients) were: teratoma (2), mesoblastical (2) and cystosis nephroma (1), disontogenical vessels tumour – fibrohaemangioma (1). Removal of benign neoformations in all cases resulted in recovery, there being neither complications nor recurrences.
Conclusions: Thus, the tumours of the kidneys in children are notable for a marked variety of morphologic structures of tumours and character of clinical manifestation.

Tumours and tumourlike formations of the great omentum in children

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Aim: Tumours and tumourlike formations of the great omentum occur rather rarely. The aim of the present study was to investigate variants of a clinical course and results of the given pathology treatment in children.
Materials and methods: From 1981 through 1997 21 children aged 3–14 years old having new masses of the given localization were treated in our clinic. The age of the majority of children (18 subjects, 85·7 per cent) did not exceed seven years and only in three cases made up nine years, i.e. 12 and 14 years old. Among all the patients 11 children had cysts (lymphangiomas), seven had verus tumours, one had a macro additional spleen of the great omentum and two had inflammatory pseudo tumours. Mesenchymoma (two cases), neuroblastoma, liposarcoma, lipoma, neurofibroma and teratoma were among solid tumours. Seventeen patients underwent a planned removal of the masses. Four children were operated on urgently. Technically the intervention was not difficult and consisted of resection of the great omentum within the intact tissues and removal of the cysts (tumours). The following histologic study testified the supposed diagnoses of the patients.
Results: Enlargement of the abdomen, a palpable tumourlike in the abdominal cavity, episodes of algesic attacks of a minor intensity and duration (12 children, 57·16 per cent) were characteristic of a noncomplicated course of the given pathology. A complicated course (nine children, 42·86 per cent) is characterized by an attack of pains in the abdomen which acquire a constant character and increase. The complication and suppuration of the cyst combined remind the acute appendicitis clinic. The follow-up of 20 patients is good. One child with liposarcoma died four months later following the operation due to dissemination of the process and an increase of tumour aggressiveness.
Conclusions: Thus, the tumours and cysts of the great omentum are notable for a marked variety of both morphologic structure of tumours and character of clinical manifestation. Because of the large size of omentum tumours a laparoscopic removal does not prove its value as the surgical technique relies on the penetration of a vacant abdominal cavity. The latter is inadmissible with the inflammatory character of these tumours. Besides the removal of the great omentum tumour, this must be followed by a thorough laparotomy to avoid metastases and by biopsy of enlarged lymph nodes.

The experience of our service in the use of the microsurgical free transfer performed on children

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General approach: The increasing number of children affected by various accidents resulting in complex traumas (usually with soft tissue losses) determined a proportional increase in the number of the treatment methods. One of the modern ways to face up such casualties is the use of microsurgical techniques.
Material and method: There are presented here eight cases – children aged between 4 and 12 years – in which we have performed: a great toe to thumb transfer; two transfers of radial forearm fasciocutaneous flaps; two transfers of latissimus dorsi muscle-cutaneous flaps; one transfer of muscle-cutaneous latissimus dorsi and serratus anterior flap; two transfers of osteo-fascio-muscular peroneal flap.
Results: For all the patients, the immediate evolution as well as the later one have been very good with the flaps' integration and morphofunctional recovery well achieved.
Conclusions: 1. There are certain situations when the free microsurgical transfer appears as the only logical method for covering certain complex and large soft tissue losses. 2. As for the subjects, the particularities linked to their age usually allow an evolution with no particular incidents, accidents or complications.

Individualized surgical strategy for hydatid cysts of the liver

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The timing and type of surgery to be performed for hydatid cysts of the liver depend upon the presentation as well as the number and position of the cysts. The present study analyses several operative solutions, ranging from simple closure to hepatic resection. In a five year period, from 1993 to 1997, 142 cases of hydatid cysts of the liver were operated. All cases had antibiotic prophylaxis but only 31 cases benefited from albendazole therapy.

After neutralisation and excision of the cyst, the residual cavity was treated conservatively or by resection. Conservative techniques consisted in: simple closure nine cases, Lagrot's procedure 31 cases, omental packing in eight cases, marsupialisation 16 cases and pericystodigestive anastomosis in 37 cases. Additional biliary drainage by T tube or biliodigestive anastomosis was used in 61 cases. Resectional techniques consisted in: left lobectomy seven cases, sectorectomy five cases, segmentectomy 18 cases, pericystectomy 10 cases, and wedge resection three cases. Additional biliary drainage was necessary only in seven cases. Overall postoperative morbidity was dominated by biliary leakage in 17 cases and residual abscesses in six cases.

Our experience might lead us to conclude that: 1. appropriate drainage of the residual cavity is the key to conservative procedures and 2. hepatic resection represents a simple solution whenever cyst localisation does not involve extended parenchymal sacrifice.

Malondialdehyde after normothermic liver ischaemia and antioxidant administration

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Aim: To measure the increase of MDA-TBARS (malondialdehyde-thiobarbituric acid reactive substances) as a marker of lipid peroxidation after normothermic liver ischaemia in patients undergoing major liver resections and to evaluate the effect of an intraoperative antioxidant infusion.

Materials and methods: This prospective randomized study comprised 40 patients, 20 of them (treatment group) were given the antioxidant infusion containing tocopherol and ascorbate immediately prior to reperfusion onset. Venous blood samples for the determination of MDA-TBARS were taken prior to ischaemia, 30 minutes after reperfusion onset and at the end of the operation. Statistical evaluation was done by Mann–Whitney– Wilcoxon test. Preoperative liver function, the extent of the liver resections and the duration of ischemia were comparable in both groups.

Results: In the control group the mean value for MDA-TBARS was 0·70 nmol/ml (standard deviation SD=0·15): this rose to 0·87 (SD=0·27) during reperfusion. At the end of the operation it had returned to the basic level of 0·70 (SD=0·17). The difference between the pre- and post-ischemic values was statistically significant (P=0·01). In contrast, the treatment group showed only a marginal increase from 0·72 (SD=0·19) to 0·73 (SD=0·21) after ischaemia (P=n.s.): at the end of the operation the values were slightly lower than initially (0·68, SD=0·22). The exclusion of patients with advanced cirrhosis (histologically proven diagnosis) made the increase in the control group more obvious [from 0·70 (SD=0·14) to 0·97 (SD=0·23), P=0·007]. The differences in the increase of MDA-TBARS between the control and the treatment group then became even more statistically significant (P=0·007).

Conclusions: In our study MDA-TBARS were increased after normothermic liver ischaemia and this increase could be reduced by intraoperative administration of antioxidants.

Percutaneous treatment of hydatid cyst under sonographic guidance: preliminary study

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This paper is a retrospective study of the first 25 cases of hepatic hydatid cysts which underwent a conservative treatment between April 1996 – December 1997. There were 12 females and 13 males with a mean age of 40·1 years (7–65), which had 31 hepatic hydatid cysts. The cysts were classified in type I and II after Gharbi's classification. In the right liver lobe were located 23 cysts and in the left liver lobe eight cysts. In two cases a pulmonary hydatidosis was associated. Abdominal ultrasound and CT scan were routinely performed. All of these 31 cysts were treated by ultrasound guided fine-needle percutaneous puncture with aspiration and instillation of sterile alcohol 95. Pre and postoperative the patients were treated with Mebendazol. They were followed up by ultrasound and CT scan examination in the second day postoperative, at 1 week and monthly. No new cysts were noted during an average follow-up of 8·7 months and maximal cyst diameter decreased with minimum 62 per cent. A single episode of reversible anaphylaxis was encountered. The mean hospital stay was 3·3 days. In this paper the indications for conservative treatment and preliminary results of this method are discussed.

Prognostic significance of p53 protein and ki-67 antigen in resected liver metastases of colorectal cancer

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Aim: To determine whether p53 protein and ki-67 expression in liver metastases of colorectal cancer could predict outcome in patients treated by surgical resection.

Background: p53 tumour-suppressor gene mutation is a late event in colorectal cancer progression and correlates with metastatisation and poor prognosis. While liver resection can be performed safely, an accurate method of staging is required to compare the results of different treatment modalities after surgery. Analysis of genetic mutations may provide additional prognostic information and help the clinician in stratifying adjuvant therapy decisions.

Methods: monoclonal antibodies (DO-7 and MIB-1) were used to detect p53 nuclear protein and ki-67 antigen respectively in paraffin-embedded archival tumours of 46 patients with resected liver metastases. A comparison of survival was performed in different groups according to the level of staining of the two parameters.

Results: The median follow-up was 69 months. From the 46 studied liver tumour specimens, 36 (79 per cent) were found to present positive p53 staining. Considered alone, p53 overexpression was not a prognostic indicator of survival. When both parameters were analysed together, a subset of patients was identified with p53 and ki-67 minimal staining: 5-year survival in this group was markedly improved (53·3 per cent vs 11·5 per cent, log-rank test P=0·139).

Conclusion: 79 per cent of liver metastases expressed nuclear p53 protein: no statistical difference of survival was found between p53 positive and negative tumours. p53 negative tumours with low proliferative activity showed a trend toward improved survival.

Hepatic hydatidosis: postsurgical radiologic control: arguments for the conservative surgery

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After conservative surgery in hepatic disease due to *E. granulosus*, there is a remaining cavity that can be quite large. Some authors have spoken about the 'residual cavity disease', referring to possible complications that can arise (bilomas, abscesses, exogen vesiculation).

Aim: To observe the volumetric evolution of the residual cystic cavity and the hepatic reexpantion after subtotal cystopericystectomy.

Material and methods: From January 1988 to December 1997, 80 cysts were operated on. Ultrasound was performed postoperatively to all patients when the drainage was purulent or bilious during more than seven days. The following ultrasound controls were done at third, sixth and ninth months and CT scan was done every year after surgery.

We consider incline cysts (IC), thinking in biped position, those in which its axis and horizontal conform an angle between 220° and 320°, semi-incline (SI) from 320° to 45° and 135° to 220°. Non incline (NI) cysts from 45° to 135°.

Results: Preoperatively mean longer diameter was 11·3 cm (4·5–27). According to CT scan after one year of surgery, the measures were: cysts lower than 10 cm (25 IC, 27 SI, 2 NI): 1·8 cm. Cysts which preoperatively diameter was between 10 and 15 cm (6 IC, 4 SI, 10 NI): 4·1 cm. Those with longer diameter bigger than 15 cm (3 IC, 3 SI): 7·8 cm.

The residual cavity reduction after surgery was 90 per cent for the cysts lower than 10 cm; 75 pr cent in those between 10 and 15 cm; and 60 per cent in cysts longer than 15 cm. There are no relapses of the parasite in the cysts cavities.

Conclusions: 1. Natural progress of the residual cavity is to involution at the same time that hepatic parenchima expands. 2. SCP is a good procedure avoiding sacrificing healthy parenchyma.

Laparoscopic liver resection compared with conventional partial hepatectomy

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Laparoscopic liver resection is technically possible, but at present careful patient selection is required. Tumour size and location are of major influence on the feasibility of a laparoscopic operation. Peroperative echography is essential in the decision making. Isolation and ligation of blood vessels and bile ducts during transparenchymal liver dissection must be performed with a proper visual control of the operating field.

We carried out laparoscopic liver resection with the ultrasound dissector in three patients. In a matched-pair analysis of retrospective data the results were compared to patients undergoing conventional hepatic resection of equivalent lesions. In one patient conversion of laparoscopic to open surgery was required. As expected, the beginning of the learning curve was responsible of a prolonged duration of operative time for the resection in the laparoscopic operated patients. Patients of the laparoscopic surgery were discharged from the hospital at five and six days when patients undergoing conventional operation after a mean of 12±5 days.

Conclusion: Laparoscopic liver resection is feasible and can be considered the first choice in some peripherically located benign lesions.

Hepatic resection and transplantation for hilar cholangiocarcinoma

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Aim: This retrospective study was undertaken to evaluate various pathological risk factors which influence the survival of patients with hilar cholangiocarcinoma after curative hepatic resection and transplantation.

Due to the rarity of this malignant tumour, its prognostic risk factors have not been sufficiently analysed in any previous reports. As such, the paucity of survival data has not previously allowed stratification by pTNM staging sufficient for the evaluation of its reliability.

Methods: During the 15 year period, 72 patients (43 males and 29 females) with hilar cholangiocarcinoma underwent hepatic resection (34 patients) or transplantation (38 patients) with curative intent. Medical records and pathological specimens were reviewed to examine the various prognostic risk factors for survivals. Survival was calculated by the method of Kaplan–Meier using the Log Rank test with adjustment for the type of surgery.

Results: 1-, 3-, and 5-year survivals after hepatic resection were 74 per cent, 38 per cent, and 10 per cent, respectively and those after transplantation were 60 per cent, 32 per cent, and 25 per cent, respectively. Univariate analysis revealed that T-3, positive lymph node, positive surgical margins, and pTNM stage III and IV were statistically significant poor prognostic factors. Multivariate analysis revealed that pTNM stage 0, I and II, negative lymph node, and negative surgical margins were statistically significant good prognostic factors.

For the patients in pTNM stage 0-II, 1-, 3-, and 5-year survivals were 80 per cent, 73 per cent, and 73 per cent respectively. For patients in pTNM stage IV-A with negative lymph nodes and surgical margins, 1-, 3-, and 5-year survivals were 66 per cent, 37 per cent, and 37 per cent, respectively.

Conclusion: Satisfactory long-term survivals can be obtained by curative surgery for hilar cholangiocarcinoma with hepatic resection and liver transplantation. pTNM stages III and IV-A should be reconsidered.

Hepatic resection for non-colorectal and non-neuroendocrine liver metastases

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Aim: The resection of liver metastases, which is most commonly performed for colorectal metastases, provides a 5-year survival of 20–30 per cent. Because of heterogeneity of noncolorectal (NCR) metastases, outcome of resection of NCR liver metastases is unknown. The aim of this study was to evaluate survival of patients undergoing hepatic resection for NCR and non-endocrine liver metastases.

Methods: From 1980 to 1997, 254 patients underwent hepatic resection for liver metastases. Thirty-three patients (13 per cent) had curative resection for NCR and non-endocrine liver metastases and form the basis of this study. There were 21 men and 12 women, with a mean age of 53 years (range 24–82). The primary tumour was digestive (n=12), genitourinary (n=11), and other (n=10). The mean number (1·9; range 1–6) and the mean size (49; range 10–100) of the liver metastases did not differ among the three groups. In the 33 patients, 36 hepatic resections were performed (three iterative resections). Eighteen patients underwent major hepatectomy (15 right, three left) and 18 patients had minor hepatectomy (nine bisegmentectomies, six segmentectomies and three wedge resections). In six cases, resection of liver metastases was associated with concomitent resection of primary tumour: pancreatectomy three, gastrectomy two, enterectomy one.

Results: There was no postoperative mortality. Morbidity occurred in three patients (8 per cent): anastomotic oesojejunal fistula, colonic fistula and hepatic failure. The actuarial survival of the overall population at 1, 3 and 5 years was 76 per cent, 36 per cent and 28 per cent respectively. The median survival was 18 months for digestive tumours, 30 months for genitourinary tumours and 24 months for the other tumours.

Conclusion: Our results showed that curative resection of NCR and non-endocrine liver metastases allows the same survival as resection of colorectal liver metastases. However, survival depends on the primary tumour and most prolonged survival are in patients with genitourinary liver metastases.

Surgical treatment of liver trauma: our experience on 51 patients

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In patients undergoing laparotomy for abdominal trauma, liver injury is present in 15 to 20 per cent of those with blunt injury, and 40 per cent of those with stab wound. Mortality after major liver trauma ranges from 20 to 60 per cent with postoperative complications occurring in up to 40 per cent of the patients. The aim of this study was to evaluate the results after surgical treatment on a series of 51 patients admitted and treated in our Institution for hepatic trauma. Trauma was penetrating in 16 (gunshot wound in nine and stab in seven) and blunt in 35 patients (motor vehicle accident in 27, other causes in eight). According to Moore classification, 12 (23·5 per cent) were grade I, seven (13·7 per cent) grade II, 19 (37·3 per cent) grade III, seven (13·7 per cent) grade IV, and six (11·8 per cent) grade V. All patients with penetrating trauma underwent surgery. Of the others, 11 were operated in emergency for presence of shock. The remaining 24 haemodynamically stable patients underwent diagnostic peritoneal lavage (DPL), sonography, CT scan and angiography (only in selected cases). Seven had a positive tap at DPL and CT scan confirmed III, IV and V grade injuries and were operated on. Of the 17 others with negative DPL, CT scan showed grade I, II and III liver injuries in 11 patients which had a conservative approach, while six with grade III, IV and V injuries after initial conservative approach, had to be operated on. Surgical treatment was in 25 patients (71·4 per cent) debridement and suture, in six patients (17·2 per cent) minor liver resection and in four (11·4 per cent) left hemiepatectomy. No deaths were observed in grade I and II trauma, while three over 19 patients died in grade III (15·8 per cent), five over seven in grade IV (71·4 per cent) and all the six patients with grade V (100 per cent). From the results of our study it can be concluded that DPL is oversensitive in the detection of small intraperitoneal blood collections, while CT scan had higher specificity and sensibility both in the evaluation and monitoring of hepatic trauma.

Qualification for liver resection using laparoscopy and intraoperative laparoscopic ultrasonography

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Total estimation of cancer advancing is often done just during laparotomy. Laparoscopy connected with laparoscopic intraoperative ultrasonography (LIOUS) let us for detail estimation of cancer spreading in peritoneal cavity organs. We introduced this method in our Department in cases with liver tumours both primary and metastatic. From March to December 1997 16 patients have been done LIOUS after general anaesthesia just before laparotomy (10 metastatic after colon and rectum surgery, six with primary changes). In four cases among 10 patients with metastases laparotomy were not done due to dissemination of the cancer. Remains six were radically operated. In the group of six cases with primary changes in two patients we found hemangioma of the liver and in four hepatoma (two of them were resectable). In every case intraoperative histopathological examinations were done.

Conclusions: Laparoscopy with LIOUS lets us precisely estimate possibility of radical treatment of tumours in the liver.

Resection of metastatic colorectal liver cancer: preliminary results of a single centre experience

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The consensus in the treatment of liver metastasis from colorectal cancer is that solitary and also multiple lesions should be resected to improve prognosis. However, a potentially curative treatment is applicable to only 10–20 per cent of all patients affected by metastatic colorectal liver cancer. We retrospectively analysed our experience focusing on surgical management and predicting factors affecting the survival of colorectal metastases.

Methods: Thirty-four patients with colorectal liver metastases underwent major, minor and atypic liver resections during a period of six years. There were 20 males and 14 females with a mean age of 57±10 years (range 39 to 74). Nineteen patients (56 per cent) underwent trans-arterial chemoembolization (TAE) before liver resection. Our study was focused on: type and stage of primary tumour; number, size and type of liver metastasis; surgical technique; resection marges; node involvement; total time of Pringle manouvre; blood transfusions; postoperative recovery and oncologic follow-up. Tumours were single in 23 and multiple in 11 patients (range 1 to 5) with a mean size of 4·9±2·9 cm (range 1·2 to 13 cm). Types of liver resections were: 12 Right Hepatectomy (RH); 3 Extended RH; 2 Left Hepatectomy (LH); 4 Extended LH; 2 Trisegmentectomy; 4 Bisegmentectomy and 7 Atypical Resections. Three patients underwent re-resections (8 per cent).

Results: No perioperative mortality was seen and no postoperative bleeding episodes were encountered. Postoperative complications were recorded in 14 patients with a total morbidity rate of 41 per cent. There were 10 cases of pleural effusion; 2 cases of atelectases with pneumonia and 2 of biliary leakage. Sixteen patients had a recurrence in the liver for a total recurrence rate of 47 per cent. Prognostic factors leading to recurrence were represented only by positive tumoral resection margins. There was an influence of type of resection (major vs atypic), number of tumours and blood transfusions on overall patient survival, however statistically not significant. In TAE group 35 per cent with high necrosis rate were noticed, however statistically not significant. Mean survival after surgery is 30 months (range 6 to 73). Overall actuarial survival is 96 per cent, 60 per cent and 23 per cent at 1, 3 and 5 years and disease-free survival at 1 and 3 years is 88 per cent and 54 per cent respectively.

Conclusions: 1. The disease-free survival is affected only by positive resection margins. Other prognostic factors such as above mentioned could, however, statistically influence the prognosis in a large patient population. 2. Preoperative TAE does not improve long-term results despite high-percentage of tumoral necrosis. 3. Long-term survival can be accomplished in selected patients if hepatic resection can be performed with reasonable risk.

Hepatic trauma: conservative treatment

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Between 1993–1997 in Bucharest Emergency Hospital were admitted and treated 221 patients with hepatic trauma; 173 (78·2 per cent) were consecutive to blunt abdominal trauma and 48 (21·7 per cent) to penetrating injuries.

The main causes leading to these trauma were: traffic accidents – 125 (56·5 per cent), (self) aggressions 68 (30·7 per cent), falls 20 (9 per cent), accidents during work eight (3·6 per cent).

Conservative treatment was applied to 66 (29·86 per cent) patients: among them, 60 (90·9 per cent) had grade I or grade II hepatic injuries.

Laparotomy was however necessary for 29 (43·9 per cent) of these patients, imposed by other abdominal injuries such as: spleen, colon, small intestine, diaphragm, etc.

There were 13 deaths (19·6 per cent) none of them being caused directly by the liver injury.

The criteria for a conservative treatment in heaptic trauma were: a) absence of peritoneal irritation at repeated clinical examination of the abdomen (performed by experienced surgeons); b) absence of major haemoperitoneum at repeated CT scanning and c) haemodynamic stability.

A developing useful criteria was in our experience the exploratory laparoscopy used for six (9 per cent) cases with multiple trauma and positive peritoneal lavage; in such cases we experienced with other patients that transportation for CT scanning could deteriorate the haemodynamic stability.

Laparoscopic vs open appendectomy for acute appendicitis: a prospective randomized trial

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Aim: The discussion about laparoscopic appendectomy has increased since introduction of MIS. To compare the laparoscopic with the open technique for acute appendicitis a prospective randomized trial was performed.
Materials and methods: 200 consecutive patients with a diagnosis of acute appendicitis were randomized to either laparoscopic (n=100) or open appendectomy (n=100) between February 1995 and November 1997.
Results: Both treatment groups were comparable in age, sex, BROCA index, previous abdominal surgery and the histological classification of appendicitis. The diagnosis of acute appendicitis was confirmed by laparoscopy in 90 patients and by laparotomy in 88 patients. Conversion from laparoscopic to open appendectomy was necessary in five patients (5 per cent) for an appendix that could not be mobilized (4) and an unsuspected small bowel perforation by a foreign body in one case. When compared to open appendectomy the laparoscopic group had more additional lesions which were discovered intraoperatively besides appendicitis (24 per cent vs 7 per cent) and shorter hospital stay (median stay: 7·54 vs 8·81 days). No statistical differences could be found with respect to wound infections (7 per cent vs 11 per cent), general complications (2 per cent vs 2 per cent), mean operating time, postoperative pain score and requirement for pain medication.
Conclusions: Under trial conditions laparoscopic appendectomy is as safe as open appendectomy. Besides the diagnostic aspect it does not provide significant advantages.

Appendicular peritonitis: laparoscopic approach in 58 patients

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Aim: The use of laparoscopy in case of acute appendicitis is still debated. We prospectively studied the benefits of a laparoscopic approach in case of complicated appendicitis with localised or generalised peritonitis.
Materials and methods: Between January 1993 and December 1997, 552 consecutive patients (patients) have been operated by laparoscopy for acute appendicitis. Among them, 58 patients presented with a peritonitis assessed by peroperative inspection, bacteriological sample and histological exam. It concerned 41 males and 17 females, mean age 37·4 years (extremes: 18–85 years); 85 per cent were classified ASA I. Surgical treatment was realised by 10 surgeons. After abdominal exploration and peritoneal lavage, a totally 'in' appendectomy was performed if it was judged technically possible.
Results: There were 36 local peritonitis (LP) and 22 generalised ones (GP). A totally laparoscopic management was possible in 34 patients (58·6 per cent) with a mean operative time (MOT) of 93 minutes. A conversion was necessary in three cases of GP (median route in two cases, Mac Burney incision in one case), in 21 cases of LP (median route in two cases) with an MOT of 108 minutes. There was no mortality in this series. Postoperatively, 11 patients presented complications (three febrile ileus, six intraperitoneal abscesses necessitating reoperation in four cases, parietal abscess in two cases). The mean operative stay (MOS) was seven days (extremes: 3–21) in absence of conversion and 12 days after conversion.
Conclusion: Our results suggest that laparoscopic treatment of appendicular peritonitis in adults is possible but difficult. It is particularly recommended in generalised peritonitis allowing in 86·3 per cent of patients an extensive peritoneal lavage and appendectomy, avoiding a large median incision. Appendicular abscess is more difficult to manage by such laparoscopic approach necessitating conversion in 58·3 per cent of patients, but usually via a right iliac incision.

Management of retroduodenal perforations complicating endoscopic sphincterotomy (ES)

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Aim: Management of retroduodenal perforation (RDP) is controversial. The aim of this retrospective study was to report our experience in the treatment of RDP.

Material and methods: From April 1996 to September 1997, 488 ES were performed consecutively. During this period, seven RDP (1·4 per cent) were detected in five women and two men of median age 82 years (52–86). The diagnosis of RDP was made either readiologically during the procedure (five cases), either clinically the day after the ES (abdominal pain: one case; temperature: one case). Nonoperative treatment (gastric tube, antibiotics, total parenteral nutrition) was initially undertaken. Surgery was indicated in case of persistence or aggravation of clinical signs[1].

Results: Medical treatment was successful in 4/7 cases. Emergency surgery was indicated in 3/7 cases for: sepsis (two cases), abdominal pain (one case); one patient deceased postoperatively at day six because of massive haemorrhage. Moreover, in three out of the four patients non-operatively treated, elective surgery for the initial disease was performed, less than 30 days after the perforation: pancreatoduodenectomy for pancreatic adenocarcinoma (six days after the RDP), repair of choledocoduodenostomy (19 days after the RDP), cholecystectomy for biliary lithiasis (29 days after the RDP). In total 6/7 patients had abdominal surgery (emergency: three cases, elective: three cases); there were no operative findings in 4/6 patients; 1/6 patient, operated on for abdominal pain, had retroduodenal biliary infiltration without macroscopic perforation; 1/6 patient, operated on for sepsis, had gross perforation repaired by interrupted suture and placement of retroduodenal drains, but deceased postoperatively.

Conclusions: RDP is not systematically associated with operative findings. Surgical treatment of RDP should be indicated on the basis of clinical criteria.

[1] Chung et al. Am Surg 1993; 165: 700–703.

Finney pyloroplasty: a reasonable alternative

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Aim: The aim of this study is to present our experience in performing Finney pyloroplasty plus truncal vagotomy as an alternative to Heineke-Mikulicz pyloroplasty plus truncal vagotomy for the managing of duodenal ulcers.

Materials and methods: In the last 10 years (1986–1996), 335 patients (243 males, mean age 57·2 years and 92 females, mean age 60·4 years) underwent truncal vagotomy accompanied by pyloroplasty for the treatment of duodenal ulcer or its complications. Finney pyloroplasty was performed in 63 patients (47 males, mean age 56·7 years and 16 females, mean age 59 years). Twenty of the operations performed for bleeding, 12 for perforation, eight for pyloric stenosis and 23 for the treatment of uncomplicated ulcer. Heineke-Mikulicz and Jaboulay pyloroplasty were performed in 263 and nine patients respectively. The choice of the pyloroplasty was made liberally according to the surgeon`s preferences.

Results: There were no major postoperative complications after Finney pyloroplasty. Postoperative mortality was nil. Although there were no specific indications to perform Finney instead of Heineke-Mikuliez pyloroplasty, we found interestingly convenient: 1) to cover the crater of a large posterior bleeding ulcer using the upper segment of the posterior wall of the Finney pyloroplasty; 2) to manage pyloric obstructions with major deformity of the area; and 3) to bypass difficulty treated post-bulbar ulcers. The main disadvantage of the technique is the difficult management of the duodenal sump in case of future gastrectomy.

Conclusions: We concluded that Finney pyloroplasty is a reasonable alternative to Heineke-Mikuliez pyloroplasty especially in managing bleeding posterior ulcers and post-bulbar ulcers.

Long-term parenteral nutrition (TPN) for short-bowel syndrome: 18 years of experience

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Bowel infarction by mesenteric vascular occlusion is often regarded as a fatal disease. Often the diagnosis of severe bowel ischemia is made during laparotomy, and then ended as exploratory laparotomy. In such case the mortality rate is 100 per cent. If radical resection therapy is carried out even at the site of almost complete small bowel infarction, survival can be achieved in some patients. The motivation to attempt treatment should be further enhanced by the observation that short bowel disease can be successfully treated, giving an acceptable quality of life for the patients.

Between 1 January 1979 and 30 September 1997 we treated 24 patients (2 patients < 1 year, 22 patients > 1 year) with short bowel syndrome (mean length of small gut 34 cm) caused by mesenteric occlusive disease; their age ranged between 4 and 78 years, and the total duration of parenteral nutrition was more than 41 000 patient-days. With a median of 1890 days, the longest individual period of parenteral nutrition was 6002 days. We show the problems of long-term parenteral nutrition, including the catheter (Type Broviac) associated and nutritional complications, with reference to the individual course of the patients.

Despite described problems, patients of all ages can return to near-normality with an acceptable quality of life with the aid of parenteral nutrition at home.

Perforated duodenal ulcer: results after emergency treatment

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Background: The number of surgical procedures for a complicated peptic ulcer disease has fallen since the introduction of the H2 antagonists and omeprazole, nevertheless several studies have demonstrated that the number of surgical procedures due to complicated peptic ulcer disease remains stable in the last years. It is accepted that 4 per cent to 5 per cent of the active peptic ulcers will perforate during its evolution. These ulcers still have a high mortality rate (average 10 per cent), depending mainly on its presentation and surgical procedure.

Aim: This is a retrospective study of our experience in the treatment of perforated peptic ulcer. We intend to establish a protocol of treatment and follow-up in order to reduce mortality and relapse of the ulcer.

Material and methods: Between January 1984 and December 1995, 100 patients having an acutely perforated peptic ulcer were operated at our institution. We considered only duodenal or prepiloric ulcers, gastric ulcers or those located beyond the third portion of the duodenum were not reviewed. Mean age was 53 years (range 17–94). We analysed morbidity, operative mortality, relapse of the peptic disease and sequelae. χ^2 was used as statistical analysis.

Results: 54 patients underwent truncal vagotomy and pyloroplasty (TVP), 35 patients were treated with simple closure of the ulcer and 11 patients underwent other different procedures. Eleven patients died (mean age 72 years, range 55–84, seven males and four females) nine of them suffered hypovolemic shock before the operation, two had a previous partial gastrectomy, nine had a previous peptic ulcer surgery (seven simple closure of a perforated ulcer, two TVP). Prognostic mortality risk factors were: age >70 years, interval between symptoms and surgery >24 h and hypovolemic shock at the time of diagnosis ($P<0{\cdot}001$). Morbidity was high (17 per cent) (wound infection, respiratory distress, pneumonia, prolonged gastric emptying). Mean follow-up was five years (range 2–7). 12 per cent of the cases relapsed, 20 per cent of the patients treated with simple suture ($n=7$) and 2 per cent of the patients treated with TVP ($n=5$).

Conclusions: 1) Worsened prognosis: patients aged >70 years, patients clinically diseased 24 h before the operation and patients suffering hypovolemic shock. 2) In the presence of risk factors major operations should be avoided (TVP), simple suture could be the proper procedure.

Sonographic diagnosis of Crohn's disease of the small bowel

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Aim: To evaluate the diagnostic accuracy of high-resolution graded compression ultrasound (GrUS) compared to enteroclysis, CT and immunoscintigraphy in small intestinal Crohn's disease (SICD).
Materials and methods: GrUS was performed in 250 patients with suspected Crohn's disease of the small intestine. The results were compared to enteroclysis, small bowel CT and 99mTc AgAb immunoscintigraphy.
Results: 184 patients proved to have SICD with enteroclysis and clinical tests. The sensitivity, specificity and accuracy of GrUS were 87 per cent, 92 per cent and 89 per cent respectively. False negative GrUS studies occurred only in early disease. Enteroclysis was more accurate, CT was more sensitive, but less specific, immunoscintigraphy had less sensitivity. In early disease (n=51) enteroclysis and immunoscintigraphy had higher sensitivity, whereas the sensitivity of GrUS and CT decreased. In advanced and active disease abscesses were detected by CT and GrUS more frequently than with enteroclysis. GrUS detected all significant luminal strictures, only smaller narrowings were missed, compared to enterolclysis. Active and inactive fistulas were both reliably demonstrated by GrUS. In detecting lymphadenopathy GrUS was superior to CT. The different gut wall layer patterns, demonstrated by GrUS, correlated well with the disease severity.
Conclusions: The diagnostic results of GrUS are similar to those obtained by CT and immunoscintigraphy. However, in early stages, enteroclysis and immunoscintigraphy are more sensitive. GrUS has the possibility to stage the disease and to detect surgical indications, thus the decision of surgical intervention can be made and the effect of the therapy could be followed without endoscopy or enteroclysis.

The addition of barium does not improve the quality of water soluble contrast radiology in adhesive small bowel obstruction

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Water soluble contrast (WSC) meal and follow through radiology can be diagnostic, therapeutic, and a predictor of the need for surgery in the management of adhesive small bowel obstruction (SBO)[1].

The aim of this study was to determine whether the addition of barium improves the quality of radiographs and could better predict the level of obstruction.

A prospective study was conducted on patients presenting with SBO having had previous abdominal surgery. They were randomized to receive either 120 ml of WSC (Gastrograffin®) (Group A) or 100 ml WSC plus 20 ml of dilute barium (Group B). Plain supine abdominal radiographs were taken at 1, 2, 4 and 6 hours, as part of a meal and follow through procedure. SBO was defined as a failure of contrast to reach the caecum at 4 hours. The clinical outcome was determined by the consultant surgeon.

The radiographs were assessed by two radiologists independently, blinded to the diagnosis and clinical outcome, and a numerical score determined using criteria for quality and level of obstruction.

Forty seven patients were randomized between September 1996 and November 1997. The radiology scores for the two groups were similar, Group A: (n=25) median = 13, range: 7–22 and Group B: (n=22) median = 13, range: 8–22. Thirteen went on to surgery, eight having adhesive SBO, four in each group. The level of obstruction found at surgery was no better predicted in Group B.

The addition of barium neither improves the quality nor the predictability of level of obstruction in the management of SBO.

[1] Chung, C.C., Meng, W.C.S., Yu, S.C.H. et al. A prospective study on the use of water-soluble contrast follow-through radiology in the management of small bowel obstruction. A.N.Z.J. Surg. (1996) 66: 598–601

Open splenectomy: is this still a valid therapeutic option?

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Aim: Growing interest has recently centred on laparoscopic splenectomy for the treatment of idiopathic thrombocytopenic purpura and spherocytosis. Among points needing further discussion are the duration of the laparoscopic procedure, postoperative morbidity and mortality and long-term results, especially in children. In this retropective study we reviewed the outcome in a series of open splenectomies and compared our results with those from reported series.

Material and methods: During the 10 years from 1987 to 1997 a total of 184 patients underwent open splenectomy; 78 had malignant hemolymphopathies and 106 had thrombocytopenic purpura or spherocytosis. Of these 106, 70 (66 per cent) were younger than 14 years old. In the 106 patients who underwent splenectomy for idiopathic thrombocytopenic purpura or spherocytosis we assessed the following variables: operative time; blood loss, transfusional requirements, morbidity and mortality, length of hospitalization and long-term outcome.

Results: Operations lasted a mean 90 minutes (range 60–120 minutes); blood losses never exceeded 150 cc and no patients needed intraoperative blood transfusions. Platelet transfusions were needed only preoperatively in patients at high risk of hemorrhage (platelets <30 000 mm^3, bleeding time >15 seconds in non-responders to preoperative immunoglobulin therapy). Mortality was nil. Morbidity in children was accounted for by minor complications (wound infections or slight pleural effusions) and in adults one case only (2·7 per cent), who had an unsuccessful splenectomy, showed a hemothorax following a thoracocentesis performed for a left pleural effusion. This was the only patient who needed a blood transfusion. The postoperative hospital stay lasted a mean nine days long-term follow-up (median 53·3 months, range 2–120) only one patient (2·7 per cent) had a laparocele. 20 per cent of the adults and 14 per cent of the children with idiopathic thrombocytopenic purpura had recurrent disease.

Conclusions: Our review shows that open splenectomy can achieve extremely satisfactory results: our patients had far better outcomes than published series (reported morbidity 6–20 per cent, intraoperative blood loss 300–500 cc and transfusional requirement 13 per cent). The good outcome after open splenectomy calls into question the reported advantages of laparoscopic splenectomy, a procedure that even in expert hands involves longer operative time, greater blood loss, morbidity and transfusional requirements, particularly disadvantageous in children.

Laparoscopic treatment of spleen simple cycts

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The task of our investigation was optimization of laparoscopic technique and evaluation of the results of laparoscopic operations in patients with symptomatic nonparasitic spleen cysts (SNPSC).

We have an experience of 24 organ preserving operations in benign lesions of spleen, five of them were performed laparoscopically. All five patients (four female and one male, aged 2±4·7 years) had long history of left upper abdominal pain. On US and CT the sizes of the cysts ranged from 5 to 12 cm. Serological tests excluded parasitic nature of the cysts. The patients have normal coagulogram and immunological status.

Laparoscopic intervention includes steps listed below: 1) Pneumoperitoneum. 2) Introduction of three trocars. 3) Puncture of the cyst and emergence cytology of content. 4) Excision of cyst's roof with its morphological investigation. 5) Hemostases and deepitelization of residual epithelial surface of cysts using 96° ethanol. 6) Washing out and drainage of operation field.

In some cases (residual cavity) we recommend to use glue and tamponade with greater omentum. The volume of operative bleeding was minimal.

Postoperative course in all patients was uneventful, on US there were no retention of fluid was found. All patients discharged in three days.

Long term results were excellent, the patients after organ preserving laparoscopic operation had no changes in immune system and hemostases in comparison with healthy control group.

Conclusion: Laparoscopic operation in SNPSC is a safe and effective procedure.

The treatment of splenic injuries: our experience

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Aim: The spleen is the most commonly affected organ in closed abdominal injuries. The management of splenic trauma has evolved towards more conservative options, as a result of diagnostic advances in the evaluation of the lesion, and resuscitation ward improvements.

Material and methods: A review was made of the clinical histories of 80 patients emergency hospitalized for splenic trauma between January 1991 and December 1997. The diagnostic procedures employed, management, the duration of hospital stay, and surgical morbidity-mortality were evaluated. A distinction was made between conservative medical treatment (non-operated patients), conservative surgery (with preservation of the spleen) and total splenectomy.

Results: Mean patient age was 32 years: 77·5 per cent were males and 22·5 per cent females. Traffic accidents were the cause in most cases (70 per cent), followed by pedestrian traffic injuries (16·2 per cent), accidental blunt trauma (7·5 per cent) and falls from a height (6·2 per cent). Echography was performed in 85 per cent, and CT in 67·5 per cent. Seven patients (8·7 per cent) underwent peritoneal punction-lavage, with hemoperitoneum in all of them. There were associated injuries in 52·5 per cent of cases. An emergency laparotomy was performed in three cases, without prior explorations, in view of the major hemodynamic instability observed. The splenic injuries were predominantly of type I (25 cases), followed by types II, III and IV (22, 17 and 16 cases, respectively). An expectant, non-surgical approach was adopted in 28 cases, while surgery was performed in the remaining 52 cases. Conservative splenic surgery was carried out in nine of these patients. Mean hospital stay was 10·5 days (10·5 and 12·4 days in the case of conservative surgery and total splenectomy, respectively), vs 14·2 days among those not operated upon. Admission to intensive care proved necessary in 37·5 per cent, with a mean stay of six days. Complications were in turn more frequent among the splenectomized patients – global mortality being 8·1 per cent.

Conclusions: The indications for conservative management are maintained, though limited by the risks involved in blood transfusion. The decision to either attempt to save the damaged spleen or remove it depends upon a precise quantification of blood loss, with a careful evaluation of splenic parenchymal losses – requirements which can only be properly met by an exploratory laparotomy. In any case, we consider that a splenectomy should be performed in the event of blood losses in excess of 1000 ml, with coagulopathy, associated lesions, involvement of the splenic hilus, or extensive splenic parenchymal damage.

Percutaneous drainage of splenic abscesses

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Pyogenic splenic abscesses are rare conditions that tend to occur in patients with predisposing factors. Splenectomy is the standard surgical treatment for these lesions. Currently, with the improvements in imaging techniques, percutaneous drainage of splenic abscesses has been demonstrated to be one of the alternative treatments in selected cases. Computed Tomography (CT) or Ultrasound (US) guided percutaneous drainage decreases patient morbidity while decreasing the amount of patient trauma and preserves the splenic tissue with its immunologic role.

Seven patients with solitary splenic abscesses had percutaneous drainage in the last three years. Abscess cultures included salmonella species in six cases and mixed bacteria in one case. After the percutaneous drainage, one patient had intra-abdominal bleeding as a complication and underwent emergency splenectomy. Other six patients tolerated the procedures very well and CT showed small residual space on the 7th, 30th and 60th day after the percutaneous drainage.

As a result, although splenectomy remains the traditional treatment for bacterial splenic abscess, CT or US guided percutaneous drainage may be appropriate in carefully selected patients.

Carcinoma of the male breast. A retrospective study

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Introduction: Breast cancer represents less than one per cent of all malignancies in males. Because of its rarity this carcinoma has not been extensively studied.

Material and methods: We have retrospectively studied 27 men with breast cancer diagnosed and treated in our Institution from January 1969 to October 1997. The clinical features, diagnosis, treatment, histological findings and follow-up are analyzed.

Results: Mean age was 62 years. The presenting symptom was a mass in 67 per cent, nipple discharge 8 per cent, pain 7 per cent, nipple involvement 7 per cent, and others 11 per cent. None of the patients had gynecomastia. The most common site of the primary lesion was centrally located.

The median delay between the onset of symptoms and seeking medical advice was 27 weeks (range 2–480 weeks).

The staging of the tumours was: stage I: 3 patients, stage IIA: 6 patients, stage IIB: 4 patients, stage IIIB: 11 patients, stage IV: 2 patients.

Modified radical mastectomy was undertaken in 20 cases and simple mastectomy with axiliar dissection in 4 patients. Radiation therapy was carried out in 2 patients, hormonal therapy in 3, hormonal and radiation therapy in 6, hormonal and chemotherapy in two, chemo and radiotherapy in 1, radio and chemo and hormonal therapy in 8. Histopathology study showed: 22 invasive ductal carcinoma, 2 papillary carcinoma, 1 lobular carcinoma. Disease free interval was 42·5 weeks.

Conclusions: Our results indicate that male breast is an uncommon malignancy that is diagnosed 10 years later than in women and in a more advanced stage of disease. Skin involvement is more usual than in women. Gynecomastia does not seem to be associated with the development of breast cancer. Lobular carcinoma is possible in men.

Treatment algorithms we use in breast cancer in women seem to be fully indicated also in men.

Prognosis of these patients is the same in male and female patients when disease specific rate are compared. It is necessary for an early diagnosis and the institution of therapy at a stage when cure may be possible.

Breast tumour hypoploidy indicates fatal outcome

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Background: There is controversy as to the value of tumoral DNA index as a prognostic factor in breast cancer.

Aim: To investigate the individual prognostic values of different ploidy classes by determining the survival of patients of each class.

Methods: The DNA indices of 182 fresh-frozen tumour samples were determined, using normal mammary tissue as internal reference, in a Coulter Epics Profile II Flow Cytometer (samples were prepared by mechanical mincing in PBS and were labelled with propidium iodide). On the basis of their DNA indices, tumours were classified as hypoploid, diploid, near-diploid, hyperdiploid, tetraploid or polyploid. The patients were monitored at six-month intervals for up to five years.

Results: No patients with diploid, near-diploid or hyperdiploid tumours suffered relapse within the study period. Of the 62 with tetraploid tumours, five relapsed, four of whom died. Of the 22 with polyploid tumours, nine relapsed, six of whom died. All the 11 with hypodiploid tumours died. The 11 hypoploid tumours were all invasive ductal carcinomas, and in all 11 the mean size of the cell nucleus was abnormally small, but these cases differed as regards other prognostic factors (tumour size, histological grade, patient age, lymph node involvement and p53, Cerb-B2 and estrogens and progesterone receptor status).

Conclusions: The prognostic value of tumour DNA index in breast cancer is enhanced when subclasses of aneuploidy are distinguished. In this study, the mortality rate was zero for diploid, near-diploid or hyperdiploid tumours, and 100 per cent for hypoploid tumours. Hypoploidy may probably be considered an independent prognostic factor.

Advantages in free flap breast reconstruction – the deep inferior epigastric perforator flap

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Breast reconstructions with autologous tissue have been established worldwide. Lower abdominal skin and fat provides abundant source of tissue for the patient desiring breast reconstruction without a silicone implant. Loss of muscular stability and a 25 per cent rate of problems with microcirculation are disadvantages of the conventional pedicled TRAM flap. Free tissue transfer with microvascular anastomosis using the inferior epigastric vessels has much better blood supply than predicted TRAM, but there is still an 11 per cent rate of partial loss and fat necrosis. Since ALLAN developed the free DIEP flap for breast reconstruction functional and cosmetic donor defect has been minimized. This new method of breast reconstruction seems to have all the recognized advantages of the free TRAM flap without sharing its inherent disadvantages.

Our experience of this technique consists of its use in the reconstruction of 32 breasts, two patients with bilateral reconstruction. Mean age of the patients was 41 years. Revision of the arterial or venous anastomosis within three days after flap transfer was necessary in two patients due to thrombosis. Due to a postoperative haematoma around the pedicle arterial and venous interposition with vascular grafts were performed in one patient. Only in this case a 10 per cent loss of skin surface occurred. In 33 DIEP-flaps a perfect vascularisation of fat and skin tissue was achieved. Since the whole abdominal musculature were left intact, functional and aesthetic result of the donor side was even better than in free TRAM flaps using muscle sparing techniques.

Flap evaluation requires meticulous dissection of the perforators through the muscle to the parent vessels. Long vascular pedicles allow either the thoracodorsal or internal mammary vessels to be used as recipient vessels. Sensitive nerve coaptation is possible since segmental cutaneous nerves run with the perforators.

The authors demonstrate the operative details of this method and will discuss their experiences along with the advantages and disadvantages for breast reconstruction with autologous tissue.

Is axillary clearance merited in all women with breast cancer?

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Aim: The necessity of axillary surgery is increasingly under question as the indication for chemotherapy broadens and the number of small, node negative tumours increases due to the screening programme. The purpose of this study was to assess the adequacy of axillary surgery in breast cancer by age and to investigate whether this consequently influences survival outcome.

Methods: All 7144 cases of histologically confirmed invasive breast cancers diagnosed from 1980–1994 in a defined geographical area were identified. From the original pathology reports was obtained tumour size, number of nodes removed and number positive. Mean follow up was 10 years. Inadequate axillary surgery was defined as removal of less than four lymph nodes.

Results: Inadequate axillary surgery was performed in significantly more women aged 65–74 years compared to younger women. The risk of death from inadequate surgery was significantly higher in women younger than 55. In contrast, older women with inadequate axillary surgery were not compromised in terms of survival.

Age	No. Nodes	5 Yr srvl	10 Yr srvl	R.H.R.	Sig.
<55	4+	73%	59%	1·00	baseline
	1–3	66%	51%	1·46	P<0·01
55–74	4+	72%	57%	1·00	baseline
	1–3	72%	57%	1·13	n.s.

Conclusions: We conclude that older women have received differential treatment of the axilla, but in this series, survival from breast cancer has not been adversely effected. Routine axillary clearance is thus not merited.

Immediate reconstruction in breast cancer surgery. 300 consecutive cases using prostheses and flaps

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Immediate breast reconstruction after cancer surgery gives the best results from the point of view of life quality. Reconstruction is necessary not only after total mastectomy but also in several cases of partial resection, i.e. central and inferior quadrantectomy.

In our department 300 consecutive cases of breast reconstruction were performed from 01/07/1992 to 30/09/1997 (91 mastectomies; 209 quadrantectomies). After partial resection we used mammaplasty like techniques sometimes associated with contralateral breast reshaping. Recently we noted better results using selective latissimus flap after central-inferior quadrantectomy (6 cases).

After mastectomy, 59 prostheses (usually permanent expander) in submuscolar pocket without other procedures and 32 muscolocutaneous flaps (25 latissimus, 7 TRAM flaps) were carried out.

Complications were: 1 expander infection during chemotherapy which required removal of implant and delayed TRAM flap; 2 liposclerosis of zone 3 in TRAM flap; 1 light cyanosis in latissimus flap resolved by hyperbaric treatment; 1 partial necrosis in superior pedicle reduction mammaplasty like technique; 1 month later debridement, wound nearing and areola by full thickness thigh graft were performed. No complication life threatening or significantly prolonging hospitalization was observed.

Length of operations and incidence of unsatisfactory aesthetic results are progressively decreasing.

On the basis of our experience and the data of other groups immediate reconstruction seems destined to be the treatment of choice in breast surgery, also for less technical problems.

Multidisciplinar oncological approach and informed consent are mandatory.

Clinical significance of collagenase-3 expression in male breast cancer

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Introduction: Collagenase-3 is a metalloproteinase that is known to be expressed by female breast carcinomas (Ogilvie et al., J Natl Cancer Inst 1985; 74: 19–27), and has a proteolytic role against some extracellular matrix components. Thus, its expression by tumours may facilitate tumoral invasion and metastasis.

Material and methods: In order to examine the potential value of collagenase-3 in male breast cancer (MBC) we have studied its expression in a group of 54 tumours from patients with MBC. Immunohistochemical assays were performed on tissue sections using the avidin-biotin method and the supersensitive system (Biogenex, San Ramon CA, USA). Curves of relapse-free-survival (RFS) and overall survival (OS) were established by the Kaplan-Meier method and compared with the log-rank test. Multivariate Cox's regression model was used to examine interactions of different prognostic factors. The mean follow-up period was 45·5 months.

Results: A total of 34 carcinomas (63%) stained positively for Collagenase-3. On the one hand: univariate analysis showed no significant association between collagenase-3 staining and tumoral size, axillary node status, histologic grade, or oestrogen receptor (OR)-status. On the other hand, multivariate Cox's regression model showed that Collagenase-3 expression was an independent prognostic factor of overall survival (P=0·01). Thus, patients with tumours that stained positively for Collagenase-3 had a higher relative risk (RR=2·19) of death than those that presented no staining (RR=0·26).

Conclusion: These results indicate that a high percentage of male breast tumours are able to express collagenase-3. In addition, this expression is associated with a more aggressive biological behaviour of male breast tumours.

Excision of perianal thrombosis and thrombosed external haemorrhoids under local anaesthesia

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Because publications about the treatment of perianal thrombosis are rare, we reviewed all patients with a thrombosed perianal varix or a prolapsed thrombosed haemorrhoid, that were excised under local anaesthesia in the years 1995 and 1996. 136 patients (average age 41 years (17–81 years), 67 males, 69 females, 14 women during pregnancy) were operated on under local anaesthesia because of a thrombosed perianal varix (99) or thrombosed prolapsed haemorrhoid (37). Five patients were operated on 2–3 days before by other physicians because of the same disorder. All patients were treated as outpatients. The wounds after excision were left to heal by secondary intention. All patients were instructed to take sitz-baths and dressings with an astringent ointment.

Postoperative complications: four patients developed a fistulous tract on the bottom of the wound and needed additional surgery, one patient had a bleeding complication, that could be treated by local measures. Seven patients developed a recurrence. In the autumn months of 1996 (for the patients operated in 1995) and 1997 (for the patients operated in 1996) a standard questionnaire regarding recurrent symptoms, long-term complications and patient's satisfaction was sent to all patients.

The results of the follow-up by questionnaire show, that the excision of perianal thrombosis under local anaesthesia is justifiable and tolerable (most patients would have the operation done again under local anaesthesia, if necessary) and has few complications.

Comparison between bilateral gluteus maximus transposition and levator plasty in the treatment of faecal incontinence

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Aim of the study: Several operative techniques have been designed for the treatment of anal incontinence. When severe incontinence has to be cured while the anal sphincter is greatly damaged and unsuitable for repair, the anal sphincter muscle has to be substituted to get sufficient results. The outcome of the two types of operative technique has been compared, i.e. when the gluteus or the levator muscle was used for substitution.

Materials and methods: During the period from 1993 to 1997, bilateral gluteus maximus transposition was performed on eight patients (four males and four females, mean age: 38 years). The lower third of the gluteus muscle was mobilized medially from the sacrum on both sides. One of the resulting flaps was split longitudinally to create a triangle with the contralateral flap around the anal canal (Devesa method). Temporary diverting stoma was created in all patients before gluteus transposition. The other type of reconstructive surgery, levator plasty was performed in 31 female patients (mean age: 55 years). Levator plasty involves creating an 'artificial sphincter' by approximation of the pubococcygeus muscle between the vagina and the anorectum – following transperineal dissection of recto-vaginal septum. This manoeuvre enhances activation of the lateral muscle fibres of the levator plate, which are usually less damaged than the external anal sphincter.

Summary of results: Following gluteus transposition, the functional rehabilitation of transposed muscle was achieved by sphincter training for additional two to three months. The stomas were closed four to six months after reconstructive surgery. Continence improved in seven out of eight cases both according to the subjective opinion of patients and the manometrical results. Mean basal pressure increased from 20 to 30 mmHg; mean squeeze pressure rose significantly, from 40 to 90 mmHg. Levator plasty improved continence in 24 out of 31 patients. By manometry, mean basal pressure increased from 30 to 45 mmHg, whereas mean squeeze pressure improved from 55 to 75 mmHg.

Conclusion: In properly selected cases – when anorectal sensation and faecal consistence are normal – the functions of the external sphincter can be substituted by gluteus transposition. Temporary diverting stoma and postoperative sphincter training are prerequisites to acceptable functional results. Levator plasty can achieve acceptable functional result as well. This procedure is less aggressive than gluteus transposition, but when the pelvic floor is severely damaged (e.g. denervated), it is unsuitable for the restoration of faecal continence.

Third degree of hemorrhoidal disease – ligature or operation

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Routine treatment of first and second degree of hemorrhoidal disease (HD) is conservative. For fourth degree treatment is commonly operative. Persisting dilemmas are about III degree: different authors are treating them with both methods, with various results. There are no clear indications about conservative or operative treatment for this degree. The aim of the study was to declare significance of pectinate line diversion as common factor determining the method of treatment.

All patients with grade III of HD (264) are divided in two groups: group A – patients with pectinate line in normal position inside anal canal (122); and group B – patients with partial or complete dislocation of pectinate line distally (142). Group A was treated with ligature by Baron, group B operatively, by Milligan-Morgan operation (122). Twenty patients from group B refused operative treatment. In group A we had good result in 91 patients (75 per cent), satisfactory in 18 (15 per cent), bad in 13 (10 per cent). In group B (operative treatment) good results in 97 (80 per cent), satisfactory 19 (16 per cent), bad 6 (4%). Patients in group B refusing operative treatment (20) were treated with ligature, but not with such good results as operative (good 0; satisfactory 11, bad 9).

Considering these results, authors are suggesting treatment of III grade of HD: when pectinate line is in place, treatment should be conservative, when dislocated pectinate line operative treatment should be applied. Also, from practical point of view, all grades of HD can be divided into two categories: 1. with pectinate line in place – conservative treatment (medicaments, IRC, ligature) and 2. with dislocated pectinate line – operative treatment.

Total mesorectal excision: results of two types of restorative proctectomy

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Aim: To evaluate the perioperative complications and postoperative function following total mesorectal excision (TME) with restorative proctectomy for rectal cancer of the lower and middle third.
Materials and methods: From 5/96 to 1/97 of 156 patients with rectal cancer 42 underwent TME with (supra-)anal colonic **J**-pouch anastomosis. Perioperative data were collected retrospectively. A questionnaire, concerning functional outcome was undertaken six and 12 months postoperatively. Good results encouraged a prospective study to compare the colonic **J**-pouch of 5–7 cm length with a lateroterminal anastomosis with a 7 cm short limb (1.7.97–1.12.97). The first group comprised 19 patients, the second 16.
Results: In the first series we saw two deep vein thrombosis, one with a non-fatal embolism. Only five patients needed protective ileostomy. There were three radiological and two clinical anastomotic leakages. The latter necessitating covering stoma. All stomas were subsequently closed. No patient died. After six and 12 months the mean stool frequency was 4·3 (3–7) and 2·5 (1–4), respectively. The incontinence score of Jorge and Wexner (0–20) had a mean value of 2·4 (0–19). The second study with a total of 35 patients showed an anastomotic leakage rate of 16 per cent (3 of 19) for the **J**-pouch and 44 per cent (7 of 16) for the lateroterminal anastomosis.
Conclusion: Functional results of deep low anterior resection with restorative proctectomy are excellent. A short colonic **J**-pouch is superior to lateroterminal anastomosis because of fewer complications.

Resection and primary anastomosis with protective colostomy as an alternative to Hartmann procedure in left colonic peritonitis

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Background: Hartmann's procedure remains the favoured option in patients with acute left colonic and sigmoid disease, despite the well documented morbidity associated with reversal. We performed a prospective study to determine whether primary anastomosis with protective colostomy constitutes a valid alternative to the Hartmann procedure.
Methods: Between July 1994 and July 1997 all patients with peritonitis due to free perforation of left colonic and sigmoid origin underwent resection and primary anastomosis with protective colostomy. Restoration of colonic continuity was programmed six weeks later, after verification of the anastomoses by gastrograffin enema. The group comprised five men and 13 women of mean age 73 years (32–97 years). Mean ASA and APACHE II scores were 2 and 12·5, respectively. The mean delay between onset of symptoms and surgery was 74 hours. Pathological examination showed diverticular disease in 17 patients and a ruptured leiomyosarcoma in 1 patient.
Results: Thirty-day mortality was 5.5 per cent (n=1) and hospital mortality was 11·1 per cent (n=2). No patients showed signs of suture disruption and routine radiological controls of all anastomoses at six weeks supported this. Mean length of hospital stay was 20±10 days. Closure of the colostomy using a small peristomal incision was performed in all surviving patients after a mean delay of 45±9 days. Mean length of hospital stay for colostomy closure was 7±3 days and this was accomplished without mortality. Outcome variables of the present group of patients were compared to those of a well-matched Hartmann control group. Mortality, morbidity and fistula rates were similar for the two groups. Duration of hospital stay and delay to stoma closure were shorter following primary anastomosis and protective colostomy ($P<0{\cdot}05$). Rates of stoma closure were higher in the primary anastomosis group ($P<0{\cdot}05$).
Conclusions: Primary anastomosis with protective colostomy is a valid alternative to the Hartmann procedure in left colonic peritonitis.

Pfannenstiel's incision in colorectal surgery

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A prospective study was undertaken between 1984 and 1987 to assess results of a transverse hypogastric laparotomy stemming from the Pfannenstiel incision in surgery of the left colon and rectum.

One hundred patients were operated on. The mean age was 61 years. Main operative procedures included: sigmoïdectomy (48), anterior resection of the rectum (24), rectopexy (12), abdomino-perineal resection of the rectum (5), total colectomy (5). Splenic flexure of the colon was mobilized in 23 patients. Four patients were operated on in one stage for colonic obstruction. Wound healing, post-operative pain and pulmonary disturbances have been evaluated.

There was no peri-operative death. Wound sepsis occurred in eight patients and hematoma in four patients. Seven patients had to be reoperated for complication by the same incision. Sixty one patients were available for follow up examination (median follow up: 75 months). There was no incisional hernia in spite of factors considered to increase the risk of parietal failure. Post operative ventilatory depression was evaluated by pulmonary function test, peak expiratory flow rate and blood gas analysis. Results were similar to those of a lower midline incision. Assessment of the post-operative pain score was made using a linear analogue scale. Requirement for analgesia was calculated. Pain was estimated moderate at 24 hours after surgery, low at 48 hours, absent at 72 hours. Analgesia was not required at 72 hours for 65 per cent of the patients.
Conclusion: The Pfannenstiel mini-laparotomy provides the greatest strength to the abdominal wall and minimizes the post operative pain and respiratory depression. It is suitable for colo-rectal surgery usually performed through a lower and upper midline incision or even a complete median laparotomy. With a combined strategy of early oral nutrition and mobilization, this incision achieves a minimally invasive, stress reducing, procedure.

Results of laparoscopic cholecystectomy

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Aim: To evaluate the results of laparoscopic cholecystectomy (LC) in the 5 years period.

Patients and methods: First LC in Lithuania was performed at our clinic in December 1992 and introduced for treatment of patients with symptomatic gallbladder disease. From December 1992 to December 1997 LC was performed in 2282 patients. Mean age 50·1 years (ranged from 14 to 88 years) among 1973 women and 309 men. 226 (5·5 per cent) of the cases were patients with acute cholecystitis.

Results: Conversion to open cholecystectomy (OC) was necessary in 77 patients (3·3 per cent). Operative complications occurred in 12 (0·5 per cent) patients: CBD lesions – in 10 (0·44 per cent) patients, bleeding from a. cystica – 2 (0·09 per cent) patients. In six patients CBD injuries were recognized at the time of operation and after conversion to OC primary ductal repair was performed. In case of bleeding from a. cystica conversion to OC and ligation were performed. Postoperative complications occurred in 64 (2·8 per cent) patients: a) local infection – in 39 (1·7 per cent) patients (subhepatic abscess – 10, phlegmona of the abdominal wall – 1, wound infection – 28), in three cases subhepatic abscess was successfully drained by ultrasound guided percutaneus approach; b) bile leakage – in 21 (0·9 per cent) patients; c) haemoperitoneum because of the bleeding: – from the abdominal wall at the trocar insertion site – in two patients; from a. cystica – one patient; d) obstructive jaundice due to stone in CBD – in 2 patients (endoscopic sphincterotomy and stone extraction was performed). There were 31 reoperations due to complications: 18 laparotomies and 13 relaparoscopies. Two patients (75 and 87 years old) died after LC – mortality 0·09 per cent.

Conclusions: To prevent iatrogenic CBD injuries correct preparation with a clear identification of the anatomic structures is essential. Relaparoscopy and ultrasound guided percutaneus drainage can be successfully used in the treatment of complications after LC.

Transinguinal diagnostic laparoscopy to evaluate presence of contralateral hernia in children

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Introduction: The incidence of indirect inguinal hernia in infants is about five per cent but the presence of contralateral patent processus vaginalis (PPV) is as high as 80 per cent and only 10 per cent of the patients evolve into a hernia.

The highest incidence of PPV is found in the first months and decrease until two years old.

Advances in laparoscopic instrumentation have permitted new applications in abdominal surgery.

Transinguinal diagnostic laparoscopy can be used to identify the presence of an indirect hernia.

Materials and methods: We described the technique that we used to contralateral inguinal exploration during the inguinal herniorraphy.

A 5 mm Port is placed into the hernia sac and fixed with a vessel loop.5–6 mm Hg pressure in Trendelembourg position. 30° laparoscope is inserted through the port and the contralateral side is evaluated. Takes no more than 3 minutes of surgery time.

Only if the evaluation is positive a contralateral repair is performed.

Results: Since 1996 we have used this procedure in all the children where we suspected a contralateral hernia with good results.

Conclusions: 1) Laparoscopic evaluation of the contralateral side via the open hernia sac is quick, safe and effective; 2) The operating time is low;
3) Transinguinal diagnostic laparoscopy may benefit the children with a suspected contralateral hernia and permit to repair during the same operation.

Laparoscopic cardiomyotomy with anterior fundoplication for esophageal achalasia and postoperative manometric assessment

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Aim: The laparoscopic cardiomyotomy with anterior fundoplication (Heller–Dor procedure) is accepted for treatment of esophageal achalasia. The aim of our study was to evaluate the effect of Heller's cardiomyotomy with Dor fundoplication on the basis of our experiences and postoperative manometric investigations.

Methods: Between December 1994 and December 1997, 19 patients with esophageal achalasia underwent laparoscopic Heller's operation with Dor's antireflux procedures. In three patients endoscopic dilatation was tried previously. Preoperative assessment involved clinical, radiological, endoscopic and manometric investigations. In all patients postoperative clinical examinations and routine manometry were performed six months later.

Results: Operation time was 35–90' (mean 55'). All patients were free from dysphagia and regurgitation during the follow-up period. Conversion to laparotomy was not required. There was one esophagus perforation requiring reoperation. Postoperative manometry in all the patients showed a decreased lower esophageal sphincter pressure (mean 12·8 Hgmm). Three of 19 patients had a normal esophageal peristalsis and 16 of 19 had hypomotility six months later.

Conclusion: Based on the obtained results which compare well with those of the literature, it could be concluded that cardiomyotomy with Dor fundoplication through a laparoscopic approach leads to good functional results and seems effective in treating esophageal achalasia.

Endoscopic resection of epiphrenic esophageal diverticula

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Epiphrenic diverticula of the esophagus are rare findings in comparison to pharyngoesophageal diverticula. The epiphrenic diverticula are mostly seen in younger patients and are accompanied with symptoms like regurgitation, mediastinal and pleural inflammation or abscesses and esophageal motility disorders.

The established surgical treatment of epiphrenic diverticula is anterolateral thoracotomy and open resection. This method goes along with severe morbidity for the patient (pulmonal complications, intercostal neuralgia, prolonged total parenteral nutrition, etc.).

A combined endoluminal and endocavital endoscopic operation to our opinion seems to be a more recent minimally invasive technique. During this procedure we localize the diverticulum intraoperatively with a flexible endoscope which also works as an esophageal splint and allows continuous endoluminal control of the margins of resection. A thoracoscopic access is used to facilitate the dissection of the diverticulum using a harmonic scalpel and to resect the diverticulum with an endostapler.

A naso-gastro-jejunal triple-lumen-tube positioned intraoperatively under endoscopic guidance allows continuous gastral decompression and early postoperative jejunal feeding. Total parenteral nutrition with all its complications and costs is made unnecessary.

Technical details of the procedure will be demonstrated as well as the perioperative management.

Laparascopic transabdominal preperitoneal (TAPP) or total extraperitoneal (TEP) inguinal hernia repair

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Aim of study: If we operate on inguinal hernia with a laparoscopic procedure, we have got two approaches for its repair. First is Trans Abdominal Preperitoneal approach (TAPP) and second is Total Extraperitoneal (TEP) one. We think that some objective criterias must be used to decide which approach is suitable.
Patients and methods: 120 patients treated by laparoscopic inguinal hernia repair between November 1994 and March 1997. Last 100 cases were included in this study. Patients mean age was 30 (16–77), all were male. Hernias classified according to Nyhus classification. TAPP carried out in 76 patients and TEP in 22 patients. Conversion to open procedure for two patients ocluded due to adhesion relating to previous abdominal operation. There was bilateral hernias in 19 of 100 patients, 11 of them were known preoperatively and eight of them were recognized in the course of TAPP laparoscopic hernia repair (14·8 per cent). Polypropylene mesh was used to reinforce for abdominal wall defect, and fixed by stapler.
Summary of results: Some minor complications such as scrotal echymosis, haematomas resolved spontaneously. Scrotal seromas were aspirated percutenously. Two port entrance wound infection were improved by dressings. Complications as ileus, subileus, and fistula were not seen. After bilateral TEP repair, Meralgia Paresthetica was seen on left thigh and improved three months later.
Conclusions: We need to choose an approach according to hernia type and patient's anatomy. We prefer the TAPP way to TAP for four conditions. First, peritoneal dissection and closure in unilateral scrotal type IIIb, IIIc, and IV are easier than TEP. Second, operative in TAPP way especially view in small and short patients is larger than TEP. Third, TAPP is useable for patients who had been operated on in hypogastric quadrant of abdomen. Fourth, if there is another disease which may be treated with laparoscopic approach we will do that with TAPP approach. When patient has got ingüinal hernia type II unilateral (maybe scrotal), type IIIa and IIIb nonscrotal and bilateral inguinal hernia we prefer TEP to TAPP. The operating time is shorter than TAPP and there is no need to enter peritoneal cavity.

We think that these criterias have to be determined exactly and could be standardized with a number of studies of laparoscopic approach techniques.

The endoscopic preperitoneal inguinal hernia repair (TEP)

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Aim of the study: The endoscopic preperitoneal hernia-plasty (TEP), described in 1993 by McKernan, combine the herniaplasty preperitoneal of Nyhus results with the advantages of the less invasive surgery, avoiding with that the risks of the transperitoneal laparoscopic access (TAPP).

We analyse our experience with the TEP technique in the treatment of inguino-crurals hernias.
Materials and methods: From November 1995 to December 1997, performed a total of 81 hernioplasties in 60 patients, 18 (30 per cent) of them by recidiva and 21 (35 per cent) bilaterals. The technique consisted in the placing of a 12 × 8 cm PROLENE mesh closing the myopectineo hole at preperitoneal level, fixed by helicosuture and under regional anesthesia.
Summary of results: Those series included 55 (91·6 per cent) men and 5 (8·4 per cent) women, with an average age of 53·6 years (between 28 and 87). The operatory time was 37 minutes (20–90) for unilaterals and 63 minutes (40–90) for bilaterals. The only intraoperatory complication was the peritoneal puncture in 11 (13·5 per cent) patients, that forced to practise 7 (11 per cent) reconversions (5 by Nyhus and 2 by TAPP). Postoperatory complications were 5 (8 per cent) seromas and 1 (1·6 per cent) recurrent hernia. The hospital stay was of about 1·6 days (1–4).
Conclusions: The TEP technique is a safe process and with an acceptable technical complexity, that allows under regional anesthesia the repair of all types of hernias. The morbidity and recurrent hernia rates are comparable with conventional hernioplasty.

Anatomy of biliary ducts and blood supply as a risk factor of the laparoscopic cholecystectomy

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Common biliary duct lying most superficially in hepato-duodenal ligament structure is easily accessible in surgery for cholelithiasis. It constitutes the basis of Calot's triangle – the area so individual that it can only be compared to a fingerprint. Laparoscopic cholecystectomy (l.ch.) in early period increased the number of biliary duct (b.d.) injury. The authors performed 50 resin casts of the liver extra- and intrahepatic b.d. and arteries in order to find the critical points in the anatomy and vascularization of extrahepatic b.d. As for the anatomy of b.d. there are two dangerous points: atypical bifurcation of hepatic ducts and long and very narrow common b.d. In the first point cystic duct situated close to vesicularis artery may be reason of its injury. In the second point overstretching of cystic duct may be the cause of c.b.d. injury, that is the most common reason for injury (three cases). We found that the origin of cystic artery and its running was externally atypical in two cases. Analysing blood supply of common hepatic and b.d. we found one case where its vascularization was extremely dependent on cystic artery. In four cases cystic duct was running close to common hepatic duct anastomosing with it very low. Dissecting cystic duct on a long part of its length can cause injury to blood supply of the lateral wall of common hepatic duct and result in necrosis with early bile leakage or late stricture. As well as using electrocautery in the region of hepato-duodenal ligament close to the common bile duct may often lead to the injury of the blood vessels of the duct which may result in the lack of blood supply and consequently in necrosis with leakage of bile or in inflammatory infiltration changes in the middle part of the duct which can result in mild jaundice. So in our examination, 20 per cent of cases showed extremely atypical anatomy creating possibilities for l.ch. complications.

Safety of laparoscopic cholecystectomy in patients with relative contraindications

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The safety of laparoscopic cholecystectomy in patients with relative contraindications (acute cholecystitis, gallstone pancreatitis and choledocholisthiasis) was evaluated in a four-year retrospective review. The study was organized as results of three groups were compared. First group was of 130 patients with relative contraindications for laparoscopic cholecystectomy (LC). The second group was of 240 LC in patients with conventional cholecystecomy and indications for operation were the same as for the first group. Operations done between January 1992 to September 1997 were included in the study. Patients were followed up three months to four years after operation. We found one lesion of common bile duct in first group – 0·76 per cent. No postoperative hernias or late complications were found. Conversion of LC in the second group was done in nine cases – 2·6 per cent. Intraoperative lesion of common bile duct was found in one case. The patient was reoperated five days after the first operation. We had no mortality or other serious complications in this group. No post-operative hernias or late complications were found. In the third group intraoperative lesions of common bile duct were registered in two cases – 0·75 per cent. Reoperations due to different reasons were done in five cases – 0·3 per cent. Postoperative complications and hernias six months after operation were found in four patients. Laparoscopic cholecystectomy in patients with relative contraindications was a safe procedure. Results showed that convertion rate, lesions of common bile duct or other late complications were not much more as in patients with no contraindications.

Symptomatic relief following laparoscopic Nissen fundoplication – does it last?

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Early experience suggested that laparoscopic fundoplication was effective. The need for longer term follow-up was apparent. Forty patients (mean age 55, range 25–74) underwent laparoscopic Nissen fundoplication by a single surgeon from January 1992 to June 1996. Mean operating time was 156 mins (range 40–270 mins) and mean hospital stay was 6.5 days (range 4–18). Mean length of follow-up was 25·2 months (range 4–54 months). Six procedures were converted to open and seven included concurrent laparoscopic cholecystectomy. Thirteen patients experienced some dysphagia during the post-operative period which was usually mild; seven of these 13 settled spontaneously and the others responded to single bougienage. 25 patients had an excellent sustained response being entirely symptom-free at latest review (mean 25·3 months, range 5–50 months). 11 had mild residual symptoms, the most prevalent of which was dysphagia. Four subsequently suffered reflux symptoms requiring medication at latest review. Two of these enjoyed symptomatic relief six and 14 months symptom-free prior to recurrence of their symptoms. This study shows that it is possible to achieve complete and lasting relief from reflux symptoms with laparoscopic Nissen fundoplication.

Prognostic value of the Dukes classification for adenocarcinoma of the stomach

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The aim of this study is to explain whether the classifications according to Dukes and Astler-Coller are helpful also in the management of gastric carcinoma. During the period from 1983 to 1993, 438 consecutive patients affected by gastric cancer underwent curative surgical treatment at I Department of Surgery of the University of Rome 'La Sapienza'. Each tumour has been staged according to Dukes, Astler-Coller's, TNM-UICC (3rd Ed – 1987) classifications on the basis of histopathological features. The level of lymph node metastases has been evaluated according to the general rules for gastric cancer by the Japanese Research Society for Gastric Cancer. The five-year survival rate (s.r.) has been determined according to the Kaplan-Meier method. All observed data were analysed by means of the chi-square test. Results were considered statistically significant at $P<0\cdot05$. The follow-up has been carried out on 406 patients. For each class of the Dukes, Astler-Coller and TNM-UICC classifications cumulative five-year s.r. were determined and compared. The five-year s.r. was 96·4 per cent in the Dukes A, 84·5 per cent in stage B, and 32·5 per cent in stage C. In the Astler-Coller's system the five-year s.r. was: 100 per cent in A, 96 per cent in B1, 84·5 per cent in B2, 45·8 per cent in C1, and 27·7% in C2. In the TNM-UICC staging the five-year s.r. was: 96·8 per cent in IA, 91·5 per cent in IB, 68·9 per cent in II, 44·1 per cent in IIIA, 18·2 per cent in IIIB, and 3·2 per cent in IV. In the Dukes classifications system there was a significant step-wise relationship between tumour stage and survival: A vs B $P<0\cdot05$, B vs C $P<0\cdot0001$. On the contrary the Astler-Coller's system showed lower correlation between stage and survival: A vs B1 p.n.s., B1 vs B2 $P<0\cdot05$, B2 vs C1 $P<0\cdot001$; C1 vs C2 $P<0\cdot005$. We conclude that the Dukes classification is a simple and easy staging system with a prognostic value also for patients affected by gastric cancer.

Results of open and laparoscopic gastric banding in the treatment of severe obesity

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The surgical treatment of morbid obesity has become routine clinical practice in many centers. Since 1991 several authors have been performing gastric banding with an adjustable band, because of both simplicity and effectiveness of the technique. A laparoscopic approach has obvious advantages in the treatment of these patients.

Patients and methods: From August 1995 till September 1997 80 patients were treated with surgical gastric banding. Preoperatively body mass index (BMI) was calculated and only BMI>35 was considered indication for operation. Initially a laparotomy was performed as part of the learning curve, but subsequently laparoscopy was intended in every patient. All patients had several dietary regimens without success. Postoperatively the frequency of adjustment of the band, weight loss, short- and long-term complications and number of reoperations were studied. Mean follow-up was 12 months (range 2-26 months).

Results: A total of 80 procedures were performed, 3 by laparotomy, 73 laparoscopic and 3 patients had a laparotomy after conversion. Mean BMI was 45 (range 36 to 57). All patients had at least one adjustment of the band (mean 1·3 times) with injection of some physiologic fluid or urografine. Vomiting occurred in all patients during the first few weeks. Complications of total dysphagia for both fluid and food was seen in 18 patients (21·6 per cent), in 8 cases a laparoscopic replacement of the banding was inevitable, while in two cases a laparotomy had to be performed with removal of the band. Conservative treatment with removing fluid from the band was possible in the other patients. Mean hospital stay was 3·3 days (range 2–6 days). Mean weight loss after 1, 6 and 12 months was 6 kg (range 0–11·5 kg), 22·3 kg (range 0–36 kg) and 27 kg (range 0–60 kg) respectively.

Conclusion: This preliminary study shows the feasibility and safety of laparoscopic gastric banding with minimal discomfort after surgery, short hospital stay and excellent short- and long-term results concerning weight loss.

Quality of life after gastrectomy for cancer: a quantitative analysis

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Aim: Surgery offers the only possibility of cure for gastric cancer (GC) patients. Since longer survivals have recently been achieved, more attention should be directed to the relief of symptoms and to the quality of life (QOL). In our study, patients were interviewed to assess whether the operative procedure was justified in terms of QOL.

Materials and methods: 73 patients operated on between 1986 and 1996 and without recurrence of disease after a minimum follow-up period of six months were studied by using a survey examining food tolerance, body weight and performance status (PS). Scores were assigned by the questioner for each response to express quantitatively the degree of physical and social well-being. The lower the score, the higher the discriminant power to indicate a good QOL. Average scores were calculated and statistical analysis was carried out to clarify whether some clinicopathological parameters may influence answers.

Results: Most patients were consuming a normal diet after operation but 57·5 per cent (42/73) were unable to tolerate the same volume of food. Eight out of 22 patients (36·4 per cent) had lost over 5 kg within 2 years of surgery and this incidence was 7/16 (43·8 per cent) more than 5 years after operation. A lower PS was present in 7/22 (31·8 per cent) and 1/16 (6·3 per cent) cases, respectively. Differences between answers did not result statistically significant according to the above mentioned variables and noticeably concerning the type of surgery.

Conclusions: The outcome after surgery is commonly based on morbidity and mortality, but little information is available regarding the QOL which is a very important endpoint in patients assessment. Our findings suggest that most patients surviving radical surgery for GC enjoy a good QOL in absence of recurrence.

Prognostic factors in node-negative gastric cancer

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Aim: The presence of lymph node (LN) metastasis closely correlates with survival of gastric cancer (GC) patients. Although prognostic value of the number and level of invaded LN has been discussed, clinicopathologic features and prognostic indicators of node negative (N–) GC patients have not yet been studied.

Material and methods: Between 1986 and 1996, 311/387 GC patients underwent surgery at our Institute (resectability rate. 80·4 per cent). After excluding 18 stump cancers, 105 out of 293 (35·8 per cent) were identified with histologically negative LN by hematoxylin-eosin staining and form the basis of our study. Patients were stratified according to several clinico-demographic and pathologic variables. Data are expressed as mean (s.d.). Kaplan-Meier survival curves were successively compared according to log-rank test. A uni- and multivariate analysis was then performed by using Cox model.

Results: Age of our patients was 66·6 (10·9) years. The number of dissected LN was 15·3 (9·2). The distribution according to depth of invasion was T1 55, T2 28, T3 22. Five-year survival rate for the whole series was 73 per cent, with a median survival of about 50 months. Serosal invasion (p 0·001), residual disease (p 0·028), non-intestinal type (p 0·031) and standard (<25 removed LN) lymphadenectomy (p 0·049) were all independent predictors of survival.

Conclusions: Our data confirm the good outcome of N-GC patients. The prognostic value of serosal invasion, residual disease and histologic type has already been discussed. Although it is initially counter-intuitive that these patients should benefit from a D2 dissection, our findings seem to point out the value of such a lymphadenectomy in that group of patients.

Surgery of gastric lymphoma

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Introduction: Despite a large number of publications within the last few years it is undoubted that many questions concerning Non-Hodgkin-Lymphoma of the gastrointestinal tract still have to be answered.

We present some preliminary results of a prospective multicenter trial from Germany.

Patients and methods: Up to January 1997 data from 403 patients suffering from the disease were collected from 154 hospitals. Treatment included operation on one hand, radiation (depending on stage and grading IF 30 Gy and 10 Gy Boost or 40 Gy abdominal bath) and/or chemotherapy (CHOP or MCO) on the other hand.

Results: 99 patients with gastric lymphoma were operated (ratio m:f=1·5:1, mean age 54·5 years [19–81 years]). Though all patients underwent preoperative upper gastrointestinal endoscopy the diagnosis was known in only 61/99 patients at the time of operation. The most frequent operative procedure was partial or total gastric resection with or without lymphnode dissection. According to the Musshoff classification 38 patients (38 per cent) were classified stage IE, 36 patients stage IIIE (36 per cent), 13 patients stage II2E (12 per cent), 6 patients stage IIIE (7 per cent) and stage IVE (7 per cent). In only 46 per cent (46 patients) a curative R0-resection could be achieved. Up to now there is no significant difference in survival between the operated patients and those who were treated by CTX or RTX (logrank test, $P=0{\cdot}64$).

Conclusion: We conclude that at the moment there is no gold standard in the therapy of gastric Non-Hodgkin-Lymphoma.

Vertical banded gastroplasty at more than five years

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Introduction: Some bariatric surgery techniques were hopeful in the short term follow up, but failed in the long term due to undesirable side effects or by insufficient weight loss. This paper shows our experience with VBG (vertical banded gastroplasty) in our first 100 consecutive patients after follow up of more than five years.

Materials and methods: Sixty patients were MO (morbidly obese) with BMI (body mass index) (kg/m^2) between 40–50 and 40 patients were SO (superobese) with BMI over 50. Initial weight was 12·565 kg (range 85–223), ideal weight 58·37 kg (range 47–83), excess weight 69·28 kg (range 38–161) and BMI 47·86 (range 37·87).

The original Mason VBG was performed in nine patients. The operation was changed to a V.L.S. (vertical line separation) because of the high rate of S.L.D. (staple-line-discruptions). This modification consisting in the complete division of the vertical line using linear staplers and a serosal patch. The TA 90 BN stapler, that simplified the operation, was used in ten patients. All pouches volumes were inferior to 20 ml. One patient died two days after re-stapling due to pulmonary embolism. Surgery was required in 25 patients, 25 per cent, due to failure of the technique (SLD, dilatation of the pouch, leaks).

Results: Change in per cent EWL (percentage of excess weight loss) is probably the easier and best measure of weight loss. The per cent EWL was 54·3 per cent and BMI 33 at five years. Individual results for our MO patients are 27 good and 29 failures, and for SO patients 13 good and 23 failures. None of the patients who got surgical benefit were able to eat a regular diet. Eleven patients (27·5 per cent) were having diets unable to eat bread or meat, 11 (27·5 per cent) diets excluding rice and fish, 7 (17·5 per cent) diets type puree and 11 (27·5 per cent) diets based on sweets. Foot intake and quality of life were affected in most patients due to the restrictive condition of the operation. We also asked patients about their satisfaction with the technique, and of those who answered, 54 were happy (67·5 per cent), 11 patients were undecided (13·75 per cent), and 15 patients (18·75 per cent) considered that the operation was negative and would not recommend it to anyone.

Discussion: The VBG operation is: 1) safe; 2) reproducible and with an easy learning curve but; 3) easily reversible by removing the band; 4) few patients had long term complications due to the technique, and 5) the stomach is easily studied by x-ray or endoscopy.

In our experience, VBG has some disadvantages: 1) *High reoperation* rate, mainly due to SLD; 2) *Quality of life* is affected, since patients are unable to eat regular food; 3) *Weight loss is inadequate*. The maximum per cent EWL occurs at two years but this loss is not generally maintained, as many patients become 'sweet eaters' and 'shake drinkers'.

Conclusions: VBG is a simple and safe technique with low mortality and minimal long term complications. The drawbacks are the high reoperation and conversion rates, poor weight loss, regaining weight and poor quality of life due to the restrictive condition of the band that can be enhanced by the use of complex operations.

The role of extended radical surgery in gastric cancer

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We define extended radical surgery in gastric cancer as: total gastrectomy + complete lymph node dissection + local peritoneal implant excision + splenectomy and distal pancreatectomy. According to some authors, radical lymph node dissection added to total gastrectomy increases the survival rates.

In between the years 1991–1997, radical extended surgery had been performed to 100 patients (61 male, 39 female) in our clinic. Ages of patients differ in between 38–73 (median age, 52). R-2 lymph adenectomy had been done in 90 cases and R-3 lymph adenectomy had been done to rest of patients. The average number of lymph node excised per operation was 40. For reconstruction, we had done 33 omega, 40 Roux-en-Y and 27 Tanner-19 eosophagojejunostomy. The median hospital stay period of patients was 10 days.

The follow up period of patients differs in between one month and six years. Since this clinical research is still continuing we can not interpretate the five-year survival rates and compare our results with the survival rates of classical total gastrectomy. But our results seem that extended radical surgery gives patient more survival chance.

Surgery of peptic ulcer in changing times

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Object of the study: Influence of the introduction of Omeprazole on surgical treatment of peptic ulcers.

Material: Between 1985 and 1996 485 patients (291 male [60 per cent] and 194 female [40 per cent]) (mean age 59 years) underwent a gastrosurgical treatment because of peptic ulcer. 29·3 per cent of the patients had gastric ulcers (n=142), 70·7 per cent had duodenal ulcers (n=343). In all 79·2 per cent of our operations (n=384) were performed under emergency conditions (56 per cent with perforation, 20 per cent with penetration, 24 per cent with bleeding ulcer); only 20·8 per cent were performed regular (n=101) 71·8 per cent of the collective had concurrent diseases (n=348).

Results: Between 1985 and 1996 the quantity of operations because of peptic ulcers was constant (figure 1) But differentiated – in relation to

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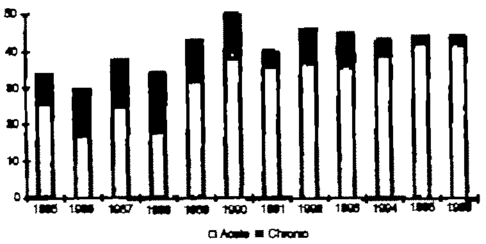

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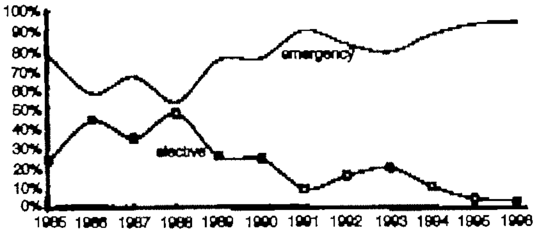

the years – the number of emergency cases increased and the number of electice indications decreased (figure 2) The favourite method of operation changed – because of the option of conservative treatment – from resective type to local excision The total complication rate was 48 4 per cent (n=235), the lethality rate 21 2 per cent (n=103) Correlations could be proved between age of the patient, comorbidity, condition under which the operation was performed (emergency or elective), hamoglobin <8 0 g/dl, size of the ulcer on the one hand and morbidity and lethality on the other

Conclusions: The introduction of Omeprazole changed the nature of operative indications for complicated ulcers Consequence was an increased number of emergency cases with rise in morbidity and lethality

Nutritional status, dietary habits, eating related symptoms and quality of life after total gastrectomy and Roux-en-Y-reconstruction

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Total gastrectomy (TG) is believed to be followed by serious nutritional consequences This study was organized to analyse the influence of this type of operation on several nutrition variables and eating-related symptoms

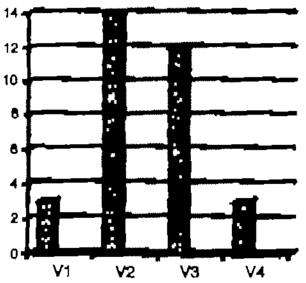
Thirty-three disease-free patients were evaluated a mean of five years after total gastrectomy for cancer The study encompassed nutritional assessment by standard anthropometric and biochemical indices, evaluation of the nutritional intake based on 24 hour recall, anamnestic analysis of postcibal symptoms and syndromes and quality of life according to the Visik and Troidl grading.

Body weight had declined progressively until the 12th postoperative month Had dropped more significantly weight loss in actual body weight/usual body weight compared with actual body weight/desirable body weight Measured tricipital skinfold, arm muscle circumference and arm muscle area had dropped not significantly less in patients undergoing TG

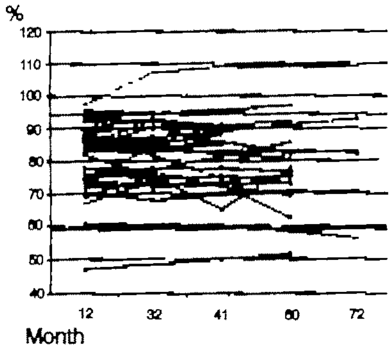
The principal symptom has been the diarrhoea (62 5 per cent), that improvement significantly to the end of 12 months (32 7 per cent) The episodes of pain or dumping were scarce

The little group of patients reported both reduced feelings of hunger and appetite Similar conclusions were observed when patients were assessed for quality of life (see figure below)

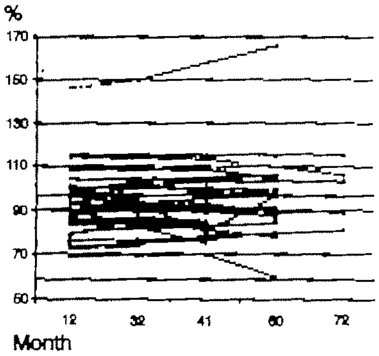
These data suggest that malnutrition after TG is relatively mild and that this operation causes only a limited impairment of the nutritional state, and spares most of the nutritional variables of clinical interest. These findings argue in favour of TG when clinically indicated without excessive concern about postoperative nutrition



Visik grading



Actual/usual body weight



Actual/desirable body weight

Laparoscopic ultrasonography reliably visualizes bile duct injuries – results of a blind randomized animal study

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Aim of the study: Only one third or less of bile duct injuries that occur during Laparoscopic Cholecystectomy are detected at the primary operation in spite of using intraoperative cholangiography. There is a need for investigation other intraoperative diagnostic methods for their possibility of detecting bile duct injuries like laparoscopic ultrasound. Detection of different bile duct injuries by laparoscopic intraoperative ultrasonography was evaluated in a blind randomized animal study.
Materials and methods: Fifty bile duct injuries were created using laparoscopic techniques in 23 farmer pigs. The number of the single lesions and the order in which the injuries were created was randomly assigned. The lesions created were: 1) Partial occlusion by a clip; 2) Complete occlusion by a clip; 3) Partial laceration; 4) Transection without clips; 5) Transection between clips; 6) Excision between clips. There were also cases without lesions. Different types of clips were used. By laparoscopic ultrasound using a flexible probe a screening of the injuries was attempted. The study was performed in a blind fashion.
Summary of results: Complete imaging of the hepatic and common bile duct from its bifurcation to the insertion in the duodenum was accomplished in all 23 animals before surgery was done. All eight cases where no lesion was performed were recognized correctly. In 48 of 49 cases the injury was diagnosed (sensitivity: 98 per cent). One injury was obvious without ultrasound. There were 44 exact diagnoses and 12 cases where injuries were recognized but could not be differentiated exactly (specificity of 100 per cent overall accuracy of 98·3 per cent). There was only one false diagnosis. The different type of clips could also be differentiated.
Conclusions: Laparoscopic ultrasonography can reliably visualize most relevant bile duct injuries. A standard for doing the ultrasound examination is proposed. Direct and indirect ultrasound signs of bile duct injuries are explained.

Supurative cholangitis in malignant biliary tract obstruction

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Aim: Cholangitis is a serious and potentially lethal disease particularly in the patients with malignant biliary tract obstruction, requiring prompt recognition and treatment. Our purpose in this study was to present the common characteristics and outcome of the patients with supurative cholangitis and to find out the factors that were closely associated with development of this serious disease in malignant biliary tract obstruction.
Patients and method: Between 1992–1997, 62 patients were operated on for malignant obstruction of the biliary tract. Of these patients 16 were found to have supurative cholangitis at laparotomy. Of the patients with cholangitis, 9 were males and 7 were females with a mean age of 62 (range 42–85 years). The cause of malignant obstruction was gallbladder carcinoma in 2 cases, cholangiocarcinoma in 5 cases, and periampullary carcinoma in 9 cases. Of these 16 patients, only one had prior operative manipulation of the biliary tree (local resection for an ampullary tumour six months ago). Twenty-three parameters were analysed to find out the risk factors that were associated with development of supurative cholangitis: a) clinical – age, sex, weight loss, fever, localization of carcinoma, b) laboratory – hematocrit, white blood count, platelet count, blood urea nitrogen, creatinine, albumin, bilirubin, SGOT, SGPT, alkaline phosphatase; c) preoperative – hospitalization time, oral intake, nasogastric decompression, positive blood cultures, blood transfusion, total parenteral nutrition, ERCP and antibiotic treatment. The chi-square analysis was employed for correlation of individual risk factors with cholangitis. Stepwise logistic regression analysis was then used to identify independent risk factors.
Results: Of the patients with supurative cholangitis, 7 (43·8 per cent) had Charcot's triad of symptoms and 1 had Reynold's pentad. Four patients (25 per cent) found to have hepatic abscesses at laparotomy. Six of 16 patients survived postoperatively and were discharged from hospital, while 9 patients died during the first hospital admission. Death was due to biliary sepsis in 5, anastomotic leakage in 2, acute renal failure in 1, and intra-abdominal hemorrhage and sepsis in 1 patient. In univariate analyses, white blood count (P=0·001), fever (P<0·01), ERCP (P<0·01), bilirubin level (P<0·01), preoperative positive blood culture (P<0·01), and preoperative hospitalization time (P<0·05) were found to have a significant correlation with the development of cholangitis. Multivariate analysis revealed that only bilirubin level, fever and ERCP were independently associated with supurative cholangitis.
Conclusion: The results of this study have shown that fever, high serum bilirubin level and ERCP performed in the preoperative period were independently associated with supurative cholangitis in malignant obstruction of the biliary tree. Since the development of cholangitis was highly lethal in malignant obstruction, identification of these risk factors may be worthwhile in the early diagnosis and treatment of the disease, and in prolongation of life.

Iatrogenic bile duct injuries – aetiology, surgical approach, prognosis

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Aim: The aim of this study was to analyse the factors affecting the success of the surgical correction of iatrogenic bile duct injuries (IBDI).
Materials and methods: During a nine year period (1988–1997) 36 patients with iatrogenic bile duct injuries were reoperated in our center. 25 of them were female and the median age was 41·7 years. At admission 3 patients had biliary fistula, 2 patients were septic and had secondary biliary cirrhosis and the rest had obstructive jaundice with cholangitis. The surgical procedures causing IBDI were cholecystectomy (17 elective, 7 emergency, 5 laparoscopic) in 29 (80·5 per cent), subtotal gastric resection in 3 (8·4 per cent), hydatid cystectomy in 3 (8·4 per cent) and repair of blunt liver injury in one (2·7 per cent) patient. IBDI were corrected by primary common bile duct repair in 5, choledochocholedochostomy in 1, choledochoduodenostomy in 9, choledochojejunostomy in 5, hepaticojejunostomy in 17 patients.
Results: 5 patients (14·7 per cent) had biliary stricture within 4–36 months 4 of whom were reoperated (hepaticojejunostomy) and one underwent balloon dilation. Two of these hepaticojejunostomy patients had recurrent biliary stricture and needed balloon dilation. The mortality and morbidity rates in this series were 8·3 per cent (3 patients) and 30·5 per cent (11 patients), respectively. The two most important factors affecting mortality and morbidity were the delay in referral and the degree of liver injury.
Conclusion: IBDI have a high mortality and morbidity rates. Therefore these patients must be referred early to a center experienced in hepatobiliary surgery.

Mirizzi Syndrome – type II

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This work presents our experience in surgical treatment of obstructive icterus which is caused by the calculus compression from the gallbladder on the hepaticohcoledochus or by prolapse of calculus through the biliobiliaris fistula.

In the period between 1992–1997, 16 patients have been operated, and a type II of Mirizzi syndrome was found present. A compression was found in 10 patients, and a bilio-biliaris fistula in 6. Analysing the clinical picture, the anamnestics data have been examined, the diagnostic procedures, the surgical procedure and postoperative complications.

In all patients, a moderate bilirubinemia has been found, of an intermittent type. By the ultrasound examination a huge calculosis has been found. The icterus without bilio-biliaris fistula, were solved by cholecystectomy, 7 cases by partial, and 3 cases by complete cholecystectomy. With bilio-billiaris fistula 3 were solved by Roux-en-Y hepaticojejunostomy, and 3 by a suture of existing defect with a T tube According to sex, there were 13 women and 3 men, according to age most of them were in their VII decade The average length of hospitalization was 10 days From the postoperative complications we had 3 wound infections

In operations for obstructive icterus it is necessary to take into consideration before and intraoperatively the possibility of an existence of Mirizzi syndrome and especially when it is impossible to separate hepatoduodenal ligament from the gallbladder. Cholecystomy and extraction of calculus make the operation easier and contribute to easier solution of the problem with decrease in intraoperative complications.

Intrahepatic sclerosing cholangitis

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Aim of the study: Sclerosing cholangitis (SC) is diagnosed by cholangiography and histology, as the clinical manifestations and laboratory parameters are nonspecific We report a case of SC of the left intrahepatic duct, and comment on the preoperative diagnosis and surgical management

Clinical case: A 69-year-old male was admitted with occasional right hypochondrial colic pain. The clinical, laboratory and radiological studies were unrevealing Abdominal CT and echography showed hepatomegaly, with dilatation of the left intrahepatic biliary tract containing echogenic images. The right intra- and extrahepatic biliary tract showed no dilatation or pathology The gallbladder was free of stones. Transparietohepatic puncture of the left intrahepatic biliary tract yielded thick bile; the bacteriological and cytological studies were negative. A decrease in caliber of the left intraheptic biliary tract was noted on day 3, with the presence of stenosis of non-tumoral appearance. MR cholangiography showed a slightly rosary-like image that was very apparent in the left intrahepatic biliary tract region. With the diagnosis of stenosis of the left intrahepatic biliary duct and intrahepatic lithiasis, surgery was performed The left liver lobe was slightly indurated, the macroscopic appearance being otherwise normal Intraoperative cholangiography showed a normal biliary tree without contrast passage into the left intrahepatic duct A left liver lobectomy and cholecystectomy were performed. The surgical piece presented a dilatation of the left intrahepatic biliary tract, which contained stones and presented periductal fibrosis. The histological diagnosis was SC

Conclusions: SC involves inflammation, fibrosis and gradual destruction of the intra- and extrahepatic biliary ducts, the latter are affected in 87 per cent of cases, while in 11 per cent and 2 per cent only the intra- and extrahepatic ducts are respectively involved The rare presentation of our case (SC limited to a small portion of the intrahepatic bile duct) led to the differential diagnosis between primary intrahepatic lithiasis and repeat cholangitis and SC

Surgical management of symptomatic biliary lithiasis during the third trimester of pregnancy

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In the past two years 1996 and 1997, 240 patients with biliary lithiasis were operated in the department of surgery and 4375 pregnant women came to delivery in the department of obstetrics. During this time, we had to operate six patients with complicated biliary lithiasis during the third trimester of pregnancy.

They were 17 to 34 years old (mean age 24·8), between 26 and 33 weeks of gestation, had non resolutive biliary colic and ultrasonographic gallstones Two of them had acute pancreatitis with an enlarged common bile duct (CBD) and increased serum amylase Open cholecystectomy was performed without cholangiography in all patients Two had preoperative endoscopic sonography confirming a free CBD Choledocotomy with extraction of CBD stones and T-tube drainage was performed in the two patients with pancreatitis All six patients recovered without surgical complication. One went in preterm labour 12 hours after operation and five went to term. All delivered healthy infants

According to the literature, complicated biliary lithiasis is not uncommon during pregnancy and biliary pancreatitis is associated with a high rate of maternal mortality and/or fetal loss Recent reports of open or laparoscopic cholecystectomy have demonstrated a favourable outcome during the second trimester When biliary lithiasis becomes symptomatic during the third trimester, our experience leads us, for the same reasons, to propose early open cholecystectomy to avoid complications of CBD stones

Early cholecystectomy is a safe procedure in patients with symptomatic biliary lithiasis during the third trimester of pregnancy

Recurrence rate of common bile duct stones is higher after endoscopic sphincterotomy than after common bile duct exploration in patients below 60 years of age: a longterm follow-up stay

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There is a tendency to treat patients with common bile duct stones younger than 60 years by endoscopic sphincterotomy and stone removal instead of surgical common bile duct exploration Longterm complications, in particular stone recurrence, after sphincterotomy in these patients are unknown. We studied retrospectively all patients below the age of 60 years who underwent endoscopic sphincterotomy (ES) or common bile duct exploration (CE) between 1978 and 1988 for common bile duct stones, focusing on early and late complications In this period 132 patients were treated, 55 by CE and 77 by ES. Follow-up was complete in 83 per cent of patients Mean (s.d.) follow-up was 11 (4) years in both groups of patients. Both groups were comparable in age, sex ratio and preoperative morbidity Two patients (4 per cent) died after CE, zero (0 per cent) after ES. Early complications occurred in 22 per cent and 18 per cent after CE and ES, respectively (P=n.s.). Duct clearance, as visualized by cholangiography, was achieved in 93 per cent after CE and in only 66 per cent after ES. In patients without duct clearance, spontaneous flow-down of stones was expected Longterm evaluation revealed 2 per cent of patients with cholangitis and 2 per cent of patients with common bile duct stenosis after ES, whereas this percentage was 0 per cent in the CE group Three years after operation, one of the 44 (2 per cent) patients in the CE group had recurrent stones, in contrast to 12 of 63 (19 per cent) patients after ES ($P<0·05$) Stones recurred on average five years after ES and were all removed by (re)sphincterotomy Stone recurrence was not due to incomplete duct clearance at the initial procedure.

It is concluded that treatment of common bile duct stones by endoscopic sphincterotomy in patients below 60 years of age, is associated with a higher incidence of stone recurrence in comparison with treatment by surgical common bile duct exploration

Surgical treatment of benign biliary obstructive jaundices

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In patients with symptomatic benign biliary obstructive jaundices, the management has been controversial since the introduction of endoscopic retrograde cholangiopancreatography

Aim: The aim of this study was to evaluate the treatment of choice that include however other surgical options.
Material and methods: We analysed in a retrospective study the actiology and the surgical techniques of 266 patients with benign biliar obstruction. Between 1989 and 1996 we had treated 210 cases of secondary choledocholistiasis (78·94 per cent), 16 cases of residual choledocholistiasis (6·1 per cent), 2 cases of primary choledocholistiasis (0·74 per cent), 13 cases postoperative strictures (4·88 per cent), 11 cases of chronic papilitis (4·13 per cent), 3 cases of hydatic cyst (1·12 per cent) and 7 cases of chronic pancreatitis (2·63 per cent).
Results: One hundred and fifty underwent T-Kehr drainage (56·39 per cent). We have performed 77 biliary anastomosis: 60 choledochoduodenostomies (22·5 per cent) and 17 hepaticojejunostomies (6·39 per cent). We had operated 13 sphincterectomies by duodenostomy (4·88 per cent) and 26 were performed by endoscopic retrograde cholangiopancreatography (ERCP).
Conclusions: Our experience indicates that laparotomy could have been avoided in many cases if ERCP could have been performed sooner. It may be in selected patients the initial surgical option for decompression in the cases of benign biliary obstructive jaundices, that make possible the placement of successful endoscopic endoprothesis in the biliary duct. However bilio-enteric bypass with a Roux-en-**Y** jejunal loop yields a superior postoperative quality of life. We believe there exists a great variety of techniques performed in the management and treatment of the benign obstructive jaundice. Thus, we have to choose the optimal surgical technique.

Surgical management of iatrogenic bile duct injuries

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Iatrogenic bile duct injuries (BDI) are the most challenging complications following gallbladder surgery. Treatment options include surgery and, recently, interventional endoscopy and radiology. The results of the latter procedures still need to be compared with the surgical ones. We have reviewed 36 patients with BDI surgically treated from 1973 to 1997. Indications and results of reconstructive surgery have been evaluated according to the time of recognition and type of lesion, which have been reclassified. 30 patients had their initial surgical repair in our institution, whereas 6 patients were referred to us after a previous attempt of repair performed elsewhere. In the latter cases a choledocoduodenostomy (4 patients), an end-to-end biliary-biliary anastomosis (1 patient) and a hepaticojejunostomy (1 patient) were the initial surgical procedures. Hepaticojejunostomy was our procedure of choice (performed in 28 cases as first attempt and in 1 case after the failure of an end-to-end repair), followed by choledotoduodenostomy. 40 operations have been performed on 36 patients. Mortality and morbidity rates were 0 and 8·3 per cent, respectively. In a median follow-up of 3·5 years, 1 biliary fistula and 2 post repair bile strictures were recorded. One patient who first underwent an hepaticojejunostomy needed two reoperations consisting of surgical dilation of anastomosis and a subsequent cholangiojejunostomy (Longmire procedure). One patient who was initially treated with T-tube placement, was operated later on with a choledocoduodenostomy for biliary stricture. Another patient after an initial end-to-end repair required an hepaticojejunostomy for biliary fistula. Because of its good results in long-term follow-up, surgery still remains the treatment of choice in most types of BDI.

Thoracoscopic management of giant bullous emphysema

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Indications for thoracoscopic treatment of bullous emphysema are identical to those for open procedures, but because video-assisted thoracoscopy (VAT) is less invasive, it can be offered to patients in poor general condition, previously considered at excessive risk for thoracotomy. Resection of compressive, space occupying, non-functional bullae, allows the re-expansion of the compressed more functional lung, improving ventilation, gas exchange with reduction of ventilation/perfusion mismatch. We describe our experience in the thoracoscopic approach to severe bullous emphysema. During the last five years, 24 patients with severe bullous emphysema (23 M and 1 F) with a mean age of 57 years (range 32 to 76 years) underwent thoracoscopic bullectomy. Mean preoperative Forced Expiratory Volume in 1 second (FEV_1) was 32 per cent ranging from 14 to 65 per cent. VAT was performed with 3 to 4 access ports. Single lung ventilation was achieved with a double lumen endotracheal tube. After complete mobilization of the lung, the bullae were resected using 35 or 45 mm endoscopic staplers. Bovine pericardial strips were used to buttress the staple lines when needed. Parietal pleurectomy was generally performed while in 3 cases, a thoracoscopic pleural tent was created to prevent an apical pleural space. Two chest tubes were usually left in place. All patients were extubated at the end of the procedure or shortly thereafter. No perioperative mortality occurred. Prolonged air-leak >7 days was the most frequent complication seen in 9 patients (37·5 per cent). Two patients had cardiac arrhythmias and 1 patient presented with self limiting bleeding requiring transfusion. Mean duration of chest drainage was 9 days (range 4 to 20 days). Mean post-operative hospital stay was 13 days ranging from 5 to 25 days. Improvements in FEV_1, although modest, reached statistical significance as did decreases in residual volumes (RV). Clinical improvement was evident in all patients. Six patients were receiving oxygen before operation. Four of these were able to discontinue oxygen therapy completely and the remaining 2 were able to reduce their oxygen need. In conclusion, thoracoscopic approach to severe bullous emphysema is safe and effective. This less invasive approach, an alternative to thoracotomy, can be offered also to compromized patients with satisfactory results and acceptable rate of complications.

Value of rethymectomy in myasthenia gravis

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Myasthenia gravis is a neuromuscular autoimmune disease, in which the thymus gland is thought to play a central role in the pathogenesis. Thymectomy is now the standard therapy. Surgical-anatomic studies indicate that thymic tissue is widely distributed in the neck and anterior mediastinum, with microscopic foci of ectopic thymus in pericapsular mediastinal fat. Persistence of symptoms in patients who have undergone previous conventional thymectomy has been attributed to microscopic thymic remnants.

Material and methods: Between 1967 and 1995 we have performed 355 thymectomies in myasthenic patients, 98 of them with thymoma. The results after surgery are: 176 remissions, 108 therapeutical-remissions, 33 patients remain unchanged, 11 are worse. There have not been perioperative mortality, but 27 patients eventually died during the entire follow-up period. Reoperations for myasthenia without thymona were done in seven patients who had incapacitating weakness after conventional trans-sternal operations. All of them were females, younger than 30 years old (II-b Osserman class) with histopathological findings of hyperplasia of the thymus, under treatment with high dose of immunosuppressive therapy (prednisone, azathioprine, cyclosporine and courses of high-dose immunoglobulin or plasmapheresis) and more than five years from the previous operation. After preoperative preparation with high dose of IGIV, a repeated thymectomy was done by median sternotomy with removal of all the mediastinal fat. Mediastinal pleura was incised bilaterally from the level of the thoracic inlet to the diaphragm and again to the phrenic nerves, anterior pericardiophrenic fat, the fatty tissue in the region of the aortopulmonary window deep under the innominate vein, pretracheal fat and the superior poles of the thymus between the thymus and the thyroid isthmus. We separated the specimen in seven blocks. All the specimens were removed and submitted to the pathologist in marked separate containers for microscopical study. Chest tubes were placed bilaterally.

Results: The microscopical studies demonstrated that six of the seven patients had multiple foci of ectopic thymus. There was no perioperative mortality but we found higher morbidity, increased operative time, and more blood loss than first elective thymectomies. Three patients needed blood transfusion. The overall regression of the symptoms and signs of myasthenia in all of our patients was high, with less incidence of crisis and decreases of dose of medical treatment needed, but none achieved a total remission after three years of repeated thymectomy.

Conclusions: Rethymectomy in myasthenic patients with poor results after initial operation, found ectopic thymic foci in the surrounding adipose mediastinal tissue in almost all patients. Reoperation in these patients improved the results but none achieved a total remission. Our data support re-thymectomy in only selected cases.

Clinical appearance, imaging approach and operative treatment of pulmonary sequestration in adults

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Pulmonary sequestration (P.S.) is a rare congenital anomaly of lung parenchyma (0·15–5 per cent of anomalies of the respiratory tract) that consists of a partial or complete separation of lung parenchyma without appropriate bronchial and vascular connections. Most of these malformations are detected and treated in infancy because of recurrent pulmonary infections or solitary masses on chest X-ray. In adults, clinical appearance is more variable. Recurrent pneumonia (30 per cent), a hemoptysis (15 per cent), chest pain or pleural effusion are the most common symptoms, nevertheless about 40 per cent of adults with P.S. are asymptomatic.

Between January 1964 and January 1997 we operated 29 patients with P.S. (14 males and 15 females, age range 18–69 years, mean age 39·6 years). We saw lower lobe (89·6 per cent) and left sided (62 per cent) predominancy, intralobar type of P.S. occurred in 65·5 per cent, extralobar type in 31 per cent, mixed type in 3·4 per cent (1 patient). A wide variety of imaging techniques were used in the diagnosis of P.S. We performed chest X-ray in all, CT-scan in 48 per cent, aortography in 27·5 per cent and MRI in 10·3 per cent of our patients. In our retrospective series only 9 cases (31 per cent) were correctly diagnosed before operation. All other patients were operated upon because of persisting cystic or bronchiectatic findings or under suspicion of malignancy.

In all cases we found an anomalous systemic artery feeding the P.S., most frequently arising from the abdominal or thoracic aorta. We also found arterial supply originating from the subclavian artery, from an aneurysm of an intercostal artery or a double supply from the internal thoracic artery. Operation consisted of resection of the pathological specimen and ligature of the feeding systemic artery. We performed lobectomy in 26, pneumonectomy in two and typical resection of left segment 8–10 in one patient. Postoperative course was uncomplicated in 96·5 per cent. After discharge from hospital all symptomatic patients were without any complaint.

P.S. is a very rare, but important disease. Next to complications like recurrent infections or haemaptysis an accidental neglect of the anomalous systemic artery can be responsible for severe intra- or postoperative bleedings. We therefore recommend considering the possibility of P.S. in cystic or tumour-like changes of the lower lobes.

Surgical treatment of myasthenia gravis: our experience based on 67 cases

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This paper reports the results of surgery and care of 67 patients treated for myasthenia gravis (MG).

Patients: Between 1980 and 1996, 67 patients were operated on because of MG. The average age was 32·4±4·6 (19–67) years. As concerns the sex distribution we had 50 women and 17 men. The average period between the first symptoms and surgery was 2·2±0·6 (0·2–6) years. The severity of the disease was classified on the Osserman scale: stage I: 9 patients (13·4 per cent); stage II/A: 35 patients (52·2 per cent); stage II/B: 19 patients (28·4 per cent); stage III: 4 patients (5·9 per cent).

Treatment: The indications for surgical treatment of MG were Osserman stage I (if the symptoms did not reduce in response to medication), II/A, II/B and III, and thymoma. In all cases, the thymus and the perithymic fat tissue were removed via a median sternotomy. Histological processing indicated no thymoma in 51 patients (76·1 per cent), and thymona in 16 patients (23·9 per cent). In 4 of the 51 MG patients without thymoma (5·9 per cent), histology revealed ectopic thymus tissue in the perithymic fat. Preoperative plasmapheresis was performed in 5 of the patients in Osserman stages II/B or III, and in one case (III/A) during the postoperative period.

Results: There were no perioperative deaths. 45 patients (67·2 per cent) could be extubated in the operating theatre, and 20 patients (29·8 per cent) within 10 hours. In 2 cases (in stage II/B), the tracheal tube could be removed within 48 hours. Control examinations were carried out after 3 months, 6 months, 1 year and 5 years. After 3 months, the remission rate was 14·6 per cent, the palliation rate was 58·2 per cent; and after 5 years these were 31 per cent and 86 per cent.

Conclusions: In the surgical treatment of MG, we consider it justified to carry out thymectomy via a median sternotomy, and removal of the perithymic fat tissue. The reason is, as our findings demonstrate, that the perithymic fat tissue may contain ectopic thymus tissue, which – if left – can cause MG symptom recurrence after surgery. Median sternotomy appears most suitable for this.

Early results of pulmonary thromboendarterectomy

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Objective: Pulmonary thromboendarterectomy is a potentially curative procedure in chronic thromboembolic pulmonary hypertension. Between June 1989 and December 1994, 109 consecutive patients underwent thromboendarterectomy at our institution. Multiple changes in the surgical concept and postoperative management have been implemented since January 1995. We report the early results of 45 thromboendarterectomy operations performed between January 1995 and September 1997.

Methods: Forty-five patients (19 females, 26 males; mean age 56 years, range 29 to 72 years) were operated using cardiopulmonary bypass, deep hypothermia and circulatory arrest periods. Preoperative NYHA functional class was III in 28 and IV in 17 patients. Preoperative pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (mPAP) were elevated to 1023±230 dynes 's' cm^{-5} and 50±13 mmHg respectively.

Results: The mean circulatory arrest time was 37 minutes (range 8 to 72 minutes). The median duration of postoperative mechanical ventilation was 38 hours (range 10 to 390 hours). The in-hospital mortality rate was 8·8 per cent (4 of 45). In 41 survivors, PVR and mPAP were significantly reduced to 319±143 dynes 's' cm^{-5} (P<0·001) and 26±11 mmHg (P<0·01) respectively. Two-dimensional echocardiography (n=25) revealed a significant improvement of right ventricular fractional shortening from 20±12 per cent preoperatively to 31±16 per cent postoperatively (P<0·05).

Conclusions: In patients with severe chronic thromboembolic pulmonary hypertension, good haemodynamic and symptomatic improvements can be achieved by pulmonary thromboendarterectomy. Based on a learning curve and by changes of the perioperative management, the operative risk can be improved to an acceptable level.

Indications, results and complications of video-assisted thoracoscopic surgery

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Aim of the study: Analyse our experience in video-assisted thoracic surgery.

Materials and methods: From January 1996 to December 1997, 173 patients (106 males and 67 females with mean age of 49 years) underwent VATS procedures with non-specific (24), tuberculous (19) or malignant pleural effusion (26), disseminated lung diseases (21), encapsulated pleural empyema (11) and clotted haemothorax (5), pneumothorax (13), peripheral lung nodules (25), pleural tumours (5), lung tumours (6), mediastinal tumours (6), lung abscess (3), sympathectomy (4), achalasia (1), foreign body (1). In 3 cases the final diagnoses were not found out.

Thoracotomy was necessary ten times for technical reasons and seven times for oncological reasons. Thoracotomy in the postoperative period was carried out in 4 cases because of persistent air leakage and 1 case developed an abscess in the thoracic wall. 1 patient died during the operation.

Conclusions: The advantages of video-assisted thoracoscopic surgery for patients include minimal operating trauma, reduced if pain, earlier postoperative mobilization, for some indications a shorter hospitalization period and required VATS could be performed using local anaesthesia.

Tracheo-bronchial resections for upper airway stenoses and tumours

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Between 1980 and 1994, 61 operations were performed because of lesions causing stenoses of the trachea, bifurcation and main-stem bronchi. The trachea was resected in 41 cases. Resection was necessitated by post-intubation or post-tracheotomy stenosis in 39 patients, and by a primary tumour of the trachea in 2 cases. Three out of the 31 upper tracheal stenoses were associated with a tracheo-oesophageal fistula. In 2 of these, closure of the fistula was combined with tracheal resection. In 4 cases, the bifurcation was resected because of the tumour. In 15 cases sleeve pulmonectomy was carried out, while in 13 and 2 cases, respectively, the right lung or the left lung was removed together with the bifurcation. In 1 case, a complete traumatic rupture of the right main-stem bronchus was recognized only in a late stage, and it was necessary to remove the upper lobe and to re-anastomose the intermediate bronchus to the bifurcation.

Four of the 61 patients died, a surgical mortality of 6·5 per cent. These patients had undergone resection for a benign tracheal stenosis in 1 case, resection of the bifurcation in 1 case, and sleeve pulmonectomy in 2 cases. In 2 of these 4 fatalities, the cause of death was a suturing insufficiency. The longest segment removed from the trachea was 5 cm. The anastomoses were sutured with 3–0 absorbable suture material with interrupted sutures. In 1 case, an early membrane-like stenosis was excised. In a further 2 cases, a 30 per cent stenosis developed in the line of the anastomosis, and this did not necessitate a re-resection.

The survival rate following resections for malignant tumours depended on the stage and the N status. T_3N_0 tumours had a 5-year survival rate of 28 per cent, while the T_3N_2 tumours survival rate was 10 per cent. With a view to preventing the occurrence of anastomotic stenoses in the postoperative period, the patients underwent routine bronchoscopy both 2 and 6 weeks following the operation.

Thymectomy for myasthenia gravis: prognostic factors and long term follow-up

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Thymectomy is considered a useful therapeutic option for patients with Myasthenia Gravis (MG). We reviewed our 25-year experience with this procedure with respect to long term outcome and analysis of prognostic factors. Between 1970 and 1996 we performed 218 thymectomies for MG. 15 patients were lost to follow up; the remaining 203 (126 females and 77 males; mean age 36·2 years) form the object of our study. 56 patients (27·6 per cent) had a thymoma. MG was graded according to the Osserman classification: 50 stage I (24·6 per cent), 79 stage IIA (39 per cent), 48 stage IIB (23·6 per cent), 20 stage III (9·9 per cent) and 6 stage IV (3 per cent). Mean duration of symptoms before the operation was 11·9 months (0·5–42 months). All thymectomies for thymoma were performed through a median sternotomy; 46 thymectomies for non thymomatous myasthenia were performed through a standard cervicotomy and the other 101 procedures were performed through a partial upper sternal-splitting incision; with this approach the resection could be extended to all the perithymic medistinal fat tissue. Operative mortality was 0·99 per cent (2 patients). Mean hospital stay was 6·4 days (7·9 days before 1980 and 4·8 after 1980). After a mean follow-up of 119 months (6 to 324 months) 67 per cent of all patients improved their clinical status (21 per cent without medications and asymptomatic; 46 per cent with reduction of medications and clinically improved by at least one stage of the Osserman classification). Favourable prognostic factors were lower stage of myasthenia, absence of thymoma, younger age and short duration of the disease. Thymectomy was effective also in patients with ocular myasthenia gravis. Thymectomy presents minimal morbidity and is effective in the management of patients with mysthenia gravis at all stages of the disease. Patients with thymoma present a less favourable outcome.

Expression of MIB-1 and the retinoblastoma gene product in thyroid tumours

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Background: MIB-1 is an antibody that reacts with a human nuclear proliferation-associated antigen (Ki-67 molecule), which is expressed in all cells that are not in the G0 phase of the cell cycle. MIB-1 expression is known to be related with the prognosis of numerous malignancies. Alterations of the retinoblastoma (Rb) tumour supressor gene and its encoded protein (RbP) have been detected in a variety of neoplasms. The aim of this study was to assess the expression of MIB-1 and RbP in several types of thyroid tumours and to analyse their interrelationships.
Materials and methods: We evaluated follicular adenomas (FA) (*n*=5), Hürthle cell adenomas (HA) (*n*=5), papillary carcinomas (PC) (*n*=5), follicular carcinomas (FC) (*n*=5) Hürthle cell carcinomas (HC) (*n*=3) medullary carcinomas (MC) (*n*=5) and undifferentiated carcinomas (UC) (*n*=5). The analysis was carried out by the streptavidin-biotin peroxidase complex on formalin-fixed paraffin-embedded tissues using monoclonal antibodies to MIB-1 (Immunotech, Marseille, France, 1:20) and human RbP (G3-245, BioGenex, San Ramon, CA, U.S.A., 1:200). For each case, a percentage of positively staining nuclei for MIB-1 and RbP was obtained by visual quantitative assessment of at least 200 neoplastic cells. Stromal and lymphoid staining were excluded from the counting process.
Results: The results (mean±standard deviation) were:

	FA	HA	PC	FC	HC	MC	UC
MIB-1	1·75±0·92	2·03±1·16	4·27±2·78	10·85±12·91	6·83±4·71	1·84±1·61	37·66±28·21
RbP	49·92±13·94	25·29±11·55	45·67±10·77	18·58±16·65	25·73±33·0	3·17±1·67	43·99±23·45

Statistically significant differences for MIB-1 (*P*=0·006) and RbP (*P*=0·005) were found comparing the several types of thyroid tumours but, the MIB-1 and RbP correlation was not statistically significant (R of Pearson=0·020, *P*=0·272).
Conclusions: These results support the idea that the retinoblastoma gene is implicated in different ways in the various types of thyroid tumours. However, alterations in the expression of the retinoblastoma protein is not related to the proliferation activity of the thyroid tumours.

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Localization studies in patients with primary hyperparathyroidism

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A retrospective study was performed to evaluate the effects of different preoperative localization techniques in patients with primary hyperparathyroidism (HPT).

48 patients underwent parathyroidectomy with primary HPT. Preoperative studies were carried out in all patients. Ultrasound (US) examination was performed in 27 cases, computed tomography (CT) in 15 patients, magnetic resonance imaging (MRI) in 13 cases, and Technetium-99m-sestamibi/Technetium-99m-pertechnetate radionuclide scintigraphy in 23 patients. 48 initial explorations and 4 reoperations were performed. A meticulous bilateral neck exploration was carried out in each patient for the identification of the 4 parathyroid glands. If parathyroid adenoma was diagnosed by frozen-section, exstirpation was carried out. If diffuse hyperplasia was diagnosed, subtotal parathyroidectomy (3 1/2) was performed.

28 of 48 patients with primary HPT had a solitary adenoma, and 1 of 48 patients had a double adenoma. 18 of 48 patients had diffuse hyperplasia of the parathyroid glands. In one patient the histological examination showed parathyroid cancer. 45 of 48 patients (94 per cent) were normocalcaemic after parathyroidectomy. One patient underwent early reoperation with removal of an ectopic gland from the mediastinum. Persistent HPT occurred in 1 patient, and recurrent HPT was noted in 2 patients. In these cases late secondary operations were performed. Sensitivity of localization studies in patients with primary HPT in our series were the following: US 74 per cent (20 of 27 cases), CT: 73 per cent (11 of 15 cases), MRI: 40 per cent (6 of 13 cases), radionuclide scintigraphy 91 per cent (21 of 23 cases).

In conclusion, the highest sensitivity rate of the preoperative localization techniques were found with the Technetium-99m-sestamibi/Technetium-99m pertechnetate scanning. The application of this radionuclide scintigraphy in combination of bilateral neck exploration can improve the cure rate, and decrease the incidence of persistent and recurrent HPT.

Parathyroidectomy for renal hyperparathyroidism: the transplant surgeon's perspective

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Aim: Up to ten per cent of patients receiving renal replacement therapy will require parathyroidectomy for secondary hyperparathyroidism. The aim of the current study was to report the management of this condition by a regional transplant unit.
Patients and methods: Between November 1994 and September 1997 thirty-four patients underwent parathyroidectomy for secondary hyperparathyroidism. The study population consisted of 20 male and 14 female patients of median age 41 years (range 10–63). Renal replacement therapy was as follows: transplant (*n*=17), haemodialysis (*n*=10) and peritoneal dialysis (*n*=5). Two patients were pre-dialysis. Twenty seven patients underwent subtotal parathyroidectomy and 7 patients had a total parathyroidectomy with re-implantation.
Results:

		Pre-operative Median (IQR)	Post-operative Median (IQR)	Statistical significance
Calcium (mmol/l)		3·03 (2·86–3·25)	2·39 (2·19–2·52)	*P*<0·05
Parathormone (pmol/l)		133 (99–150)	3·4 (0·9–11·1)	*P*<0·05
Alkaline phosphatase (IU/ml)		181 (121–237)	103 (63–152)	*P*<0·05
Symptoms	Bone pain (%)	17 (50%)	2 (6%)	*P*<0·05
	Pruritus (%)	9 (26%)	2 (6%)	*P*<0·05

At a median follow-up time of 12 months (range: 1–33) all patients are normolcaecaemic. All patients with functioning grafts have normal parathyroid hormone (PTH) levels however six on haemodialysis have mildly elevated PTH (0 per cent vs. 35 per cent, *P*<0·05).
Conclusion: Parathyroidectomy is effective in correcting the calcium biochemistry dysfunction seen in patients with chronic renal failure. Patients with renal transplants have a superior outcome compared to those on dialysis.

Diagnostic procedures and surgical treatment for insulinoma

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Aim of the study: In a retrospective study we analysed the efficacy of preoperative and intraoperative diagnostic procedures for detecting insulinoma and reviewed the surgical procedure in a series of 30 consecutive patients.
Material and methods: Thirty patients (14 men, 16 women, mean age 43·7, January 1988–March 1997) underwent preoperative diagnostic procedures to localize the insulinoma: ultrasonography (US) in 19, computed

tomography (CT) in 23, magnetic resonance imaging (MRI) in 24, selective angiography in 8, arterial stimulation venous sampling (ASVS) and Octreoscan in 21 cases. Most patients (28/30) underwent intraoperative ultrasonography. To determine the sensitivity and diagnostic accuracy of the preoperative and intraoperative localizing procedures, including surgical palpation, we compared these findings with the surgically-proven site of the insulinomas. Twenty-three patients underwent tumour enucleation, 6 distal pancreatic resections and one multiple hepatic biopsies. In the last two patients who underwent enucleation of insulinoma of the pancreatic head, we protected the resection site with a jejunal loop.
Results: In 28 (93·3 per cent) of the 30 patients with clinically-suspected pancreatic insulinoma the tumour was found at surgery. In one patient laparotomy disclosed liver micrometastases without a palpable pancreatic neoplasm. In another patient a hyperplastic lymph node had been mistaken for a tumour. Preoperative US, CT, selective angiography and MRI sensitivity was respectively 5·2 per cent, 18·1 per cent, 28·5 per cent and 78·2 per cent. ASVS achieved the best overall preoperative diagnostic results (sensitivity and diagnostic accuracy 90·4 per cent) whereas Octreoscan achieved only 68·1 per cent diagnostic accuracy. Surgical palpation identified 29 of 30 growths: two were false positive results (a cyst in the pancreatic head and a lymph node in the tail): therefore yielding 93·3 per cent diagnostic accuracy. Intraoperative ultrasonography (IOUS) localized 26 of 28 tumours (sensitivity 96·1 per cent) with one false positive result (diagnostic accuracy 92·8 per cent). Operative mortality was 3·3 per cent and morbidity 23·3 per cent (26 per cent in the group of patients treated with tumour enucleation).
Conclusions: These findings confirm that no single diagnostic imaging modality is reliable for localizing insulinoma. We therefore suggest the combined use of MRI, ASVS and IOUS. In our experience what is radiologically visible may not be palpable; what is radiologically visible and palpable may not be the tumour, and tumours may be neither radiologically visible nor surgically palpable. ASVS provides particularly useful information that helps the surgeon to plan the manual palpation and intraoperative ultrasonography.

Quality control in thyroid surgery: the concept of invasivity

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Is a short, targeted measure less invasive than a prolonged, exploration? In what way does routine thyroid surgery do any functional harm to the parathyroid glands? In this self-assessment approach referring to oncoming quality control standards, four comparably experienced surgeons working with different strategic approaches were given 'points' on an ordered scale of so-called 'invasivity', while doing 100 routine, non-selected, non-randomized thyroid operations in a clinic with good endocrine surgery experience (600–800 thyroid-related operations per year). In a second step, a simple invasivity index was made up: We considered: Invasivity score = 'points' × (volume of thyroid pre OP) × 1/(volume of thyroid post OP) × S for sex, with S=1 if female or 2 (male). This score was then correlated to calcium levels pre- and post operation.

There was no significant correlation between score and eventual postoperative calcium depression. 'Invasivity' did not seem to affect the postoperative calcium regulation.

We propose to discuss the definition of surgical invasivity in the intention to postulate good parametric quality control approaches in endocrine surgery.

Adrenal incidentalomas: criteria for endoscopic removal

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Objective: Adrenalectomy is not a frequent operation. Therefore the newly developed laparoscopic approach is sporadically performed by surgeons dealing with endocrine disorders. We report the results of a multicentric survey and analyse the criteria followed to decide which 'non-functioning' adrenal tumours, discovered incidentally (the so called *incidentalomas*) are to be removed. The criteria being: 1) non-secreting adrenal lesion; 2) diameter larger than 4 cm or increase in size at any re-evaluation; 3) CT scan picture of intratumoral necrosis, haemorrhage or irregular margins; 4) high dehydroepiandrostenedione (DHEAS) level.
Material and methods: Prospective evaluation of 65 videoendoscopic adrenalectomies performed on 63 patients by four surgical teams from the Belgian Group for Endoscopic Surgery (BGES) between October 1993 and October 1997.
Results: Indications for endoscopic adrenalectomy were pheochromocytoma (*n*=23), primary hyperaldosteronism (*n*=18), Cushing's adenoma or disease (*n*=7), single metastasis from adenocarcinoma (*n*=3), adenoma with DHEAS or cortisol hypersecretion (*n*=3), ACTH secreting metastases from a thymoma (*n*=1), non-secreting adenoma (*n*=8). Of the 65 adrenalectomies performed, 36 were of the left gland, 25 of the right and two bilateral. Laparoscopic adrenalectomy was successful in 61 patients (97 per cent). Median tumour size was 4 cm (range 1·5–12), median operation duration 100 minutes (range 59–360), median postoperative stay 4 days (range 2–13). Only one patient required blood transfusion.

Adhering to the proposed criteria allowed us to identify correctly 88 per cent of clear cut indications for adrenalectomy i.e., pheochromocytoma, Conn and Cushing syndromes, high DHEAS and tumours (sensitivity 100 per cent, positive predictive value 87 per cent, accuracy 88 per cent). The incidence (13 per cent) of rather debatable indications (i.e. incidentalomas) in the current series is low compared with other recent large series.
Conclusions: Endoscopic adrenalectomy can safely be performed – even sporadically – by surgeons well versed in adrenalectomy techniques for endocrine disorders and trained in endoscopic surgery. Criteria proposed to decide which incidentalomas are to be operated allow to reduce the debatable indications for adrenalectomy to 13 per cent (8/63).

Analysis of the ret proto-oncogen in families with multiple endocrine neoplasia type 2A

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Introduction: Multiple endocrine neoplasia type 2A (MEN 2A) is an autosomal dominant genetic syndrome characterized by medullary thyroid carcinoma, phaeocromocytoma and hyperparathyroidism. The application of linkage analysis led to the linkage of MEN 2A to a centromeric chromosome 10 locus and recently specific mutations in exon 10 and 11 of the RET proto-oncogen have been identified in this syndrome. The objective of this study is to evaluate clinical screening as compared with DNA analysis in diagnosis of MEN 2A in 6 families treated in our hospital.
Methods: Forty-six members of six families with MEN 2A were screened for RET proto-oncogen exon 10 and 11 mutations.

- DNA was extracted from peripheral blood samples
- Exons 10 and 11 were amplified separately by polimerase chain reaction (PCR)
- Detection of mutations by single strand conformation polymorphism (SSCP)
- Analysis of the sequences using ABI-PRISM Dye Terminator.

Results: Twenty-five individuals had mutations of codon 634, whereas 21 unaffected individuals had no abnormalities. Five of 25 individuals were of unknown status. Four of these children had thyroidectomy based on this analysis and were found to have medullarr carcinoma.
Conclusions: We concluded that RET mutational analysis is a cost-effective and accurate method for determination of gene carrier status in MEN 2A. The advantages of genetic screening to predictive testing led to substantial changes in carrier risk for many individuals we tested, which suggest that DNA analysis should be introduced in the screening programme of MEN 2A families, bringing many advantages in comparison with traditional biochemical test.

Our experience in genetic screening for multiple endocrine neoplasia type 1

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Introduction: Multiple endocrine neoplasia type 1 (MEN 1) which is also referred to as Wermer's syndrome is an autosomal dominant familial disorder characterized by tumours in parathyroid glands, pancreatic islet cells and the anterior pituitary. In addition to these tumours, adrenal cortical, carcinoid and lipomatous tumours has also been described. Screening in MEN 1 is difficult because the clinical and biochemical manifestations in members of any one family are not similar, and because of age related penetrance. In order to improve this situation biochemical screening tests need to be repeated periodically in all the members of the family.

In recent years, important advances in endocrinology have resulted from the application of molecular biology. Application of these techniques have made it possible to localize in chromosome 11q13 the gene causing MEN 1.

Material and methods: We have studied 26 patients from an affected family, 15 women and 11 men, all presenting with hyperparathyroidism. 50 per cent with cortical adrenal tumours, in four cases presenting with pancreatic tumours and in two, anterior pituitary tumours.

This is the method we have used:

- DNA was extracted from peripheral blood.
- Use of PCR (polimerase chain reaction) RFLP's (restriction fragment length polymorphism) and microsatellite polymorphism as genetic markers.
- Segregation analysis to establish MEN 1 haplotype.
- Indirect diagnosis of gene carriers depending on the haplotype inheritance.

Results: We observed an association between the MEN 1 haplotype in this family in all the known affected patients and in the last generation 8 young members of the family presented with the same haplotype and are considered as gene carriers.

Conclusions: These DNA studies enable carriers of the mutant MEN 1 gene to be detected within a family and thereby identify those individuals who need to undergo repeated screening test for the development of tumours. This technique has substantially altered the screening strategy. DNA analysis should be introduced in the screening programme of MEN 1 families.

Multimodal treatment of bony metastases in differentiated thyroid cancer

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Bone metastases (BM) from differentiated thyroid cancer (DTC) are a rare event, but represent an adverse prognostic factor with a potential fatal course. The standard modality of treatment consisting of total thyroidectomy (TT) followed by radioactive iodine therapy (RIT) is often not curative.

Of 174 patients with DTC seen in our Division from January 1992 to June 1997, 17 (9.7 per cent) had BM in one case with associated lung involvement. There were 14 females and 3 males with mean age of 60·1 years (range 39–74), but only 6 patients were under 60. TT was performed as the initial operation in 13 cases, one also underwent a unilateral neck dissection for clinically evident cervical node involvement. In addition one patient had simultaneous rib resection for a huge BM. Three patients, having previously undergone partial thyroidectomy in other institutions, years before, for conditions classified as benign, were referred to us for completion thyroidectomy and treatment of multiple BM. One patient with locally advanced DTC, diagnosed by fine needle aspiration biopsy, could not be operated on for severe cardiovascular disease and had been treated by RIT alone. Seven patients presented neoplastic fracture, five with a femara and two humera respectively. Of these patients, four had been submitted to bone replacement with metal prosthesis after one or more treatments with RIT, the others, not suitable to major surgery, were treated with intramedullary nailing and RIT. 12 patients presented BM simultaneous to DTC, while 5 developed BM years after the primary procedure, none of these patients had the correct diagnosis at the time of primary operation, multiple bone involvement was present. Histological examination of resected specimens, showed follicular carcinoma in 10 cases (58 per cent), insular cancer in 2 patients (11 per cent), Hurtle cell carcinoma in 2 patients (11 per cent) and 2 cases of papillary cancer (11 per cent) with a case of tall cell variant. In 1 case the histological diagnosis was unknown. The survival rate was very low, 3 patients died within a mean of 31 months after the diagnosis. The others are alive, mostly with disease after a mean follow-up of 21 months. From the analysis of this series, we conclude that BM from DTC carries a poor prognosis and new modalities of therapy may be needed. At the present time the surgical treatment of the bone lesion, whenever possible, followed by RIT is the treatment of choice for all patients.

Multiple endocrine neoplasia type 2A. Study of 96 members of 5 families

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Multiple endocrine neoplasia type 2A (MEN 2A) is an autosomal dominant inheritance disease, characterized by the occurrence of medullary thyroid carcinoma (MTC), pheochromocytoma and hyperparathyroidism. Increased calcitonin hormone (CT) indicates C-cell disorder. Annual testing of family members, with stimulus of CT secretion by calcium and pentagastrin, has been used routinely for diagnosis of the tumour for many years. This procedure is associated with bothersome side effects, and some family members have refused repetitive testing. After 1987 the genetic analysis of chromosome 10 was introduced and presymptomatic prediction of disease susceptibility became feasible by indirect test and latter direct predictive test by study of the mutations in the RET protooncogene. Family members who had RET mutation would be candidates for thyroidectomy and members without RET mutation could be assured that neither they nor their descendants would develop the disease.

Material and methods: Between 1974 and 1997 we studied 96 members of 5 families, 47 of them accepted the annual test for detecting elevated CT, 15 of them were operated upon for MTC (group A). After 1990 we started the study of the RET protooncogene mutation in 20 members with 12 positives (group B). During these 22 years we performed 27 total thyroidectomies with central zone lymph node dissection, 10 unilateral cervical lymph node dissection and one bilateral cervical lymph node dissection. Before thyroidectomy we performed 9 adrenalectomies for pheochromocytomas and one subtotal parathyroidectomy with forearm autotransplantation (Well's operation) for hyperparathyroidism. A total of 29 patients of the 5 families refused any study.

Results: We found that in group A (CT), 15 patients with MTC had elevated CT levels, between 720 and 10000 pg/ml, with a mean of 6600 pg/ml (normal <250 pg/ml). 11 patients had macroscopic tumour, 3 microscopic and 1 hyperplasia of C cells, 10 of them were lymph node positive. During postoperative follow-up, 8 deaths from metastases were seen and 2 had elevated postoperative CT levels. In group B (genetic study) 12 had elevated CT levels between 180 and 3500 pg/ml mean 930 pg/ml, 5 patients had macroscopic tumour, 5 microscopic and 2 had hyperplasia. Positive lymph nodes were observed in 5 cases. When we reject the so called 'guide patients' in the genetic group, we found only 1 patient with macroscopic tumour, 5 with microscopic tumour and 2 with hyperplasia. Only one patient had positive lymph nodes. In the postoperative follow-up we had only one patient with elevated CT. Of the 20 case with genetic study, eight members were negative and were eliminated of the study along with their descendants.

Conclusions: In our patients, we found the genetic study for detection of presymptomatic cases of high value because it gives the possibility to exclude members of the kindred without disease and improves the success rate for affected members. Some members refused any test for prediction of disease.

Reconstruction of the external ear throughout radial forearm fasciocutaneous free flap

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General approach: The absence – congenital or post-traumatic – of the external ear may produce an important aesthetic discomfort.

In practice there are several methods of reconstruction most of them usually using the temporal skin.

In cases of skin with multiple scars, some other method of reconstruction must be found.

Material and method: The case of a 27-year-old patient with post-traumatic absence of the entire right external ear is presented here. The scars in the area made impossible the use of the skin for reconstruction.

Reconstruction of the external ear by using a free microsurgical transfer of radial forearm fasciocutaneous flap was performed.

After the integration of the flap, modelling with silastic was accomplished in several consecutive stages.

Results: The immediate evolution of the flap was very good with its complete integration.

In the long term, after modelling, we succeeded in obtaining an acceptable external ear in both form and dimensions.

In conclusion, we presume that the technique used could be regarded as a possible new technique for reconstruction of the external ear.

Parotid adenolymphoma: improving preoperative diagnosis and subsequent surgical management

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Aim: This study (1985–1995) reviewed the role and results of FNAC in the diagnosis of adenolymphoma and examined methods of improving these results.

Methods: Review of cytological smears paid particular attention to features of infarction and squamoid metaplasia. Case note review concentrated on controversies in surgical management.

Results: Of 222 epithelial neoplasms of the parotid 33 were adenolymphomas. FNAC was performed preoperatively in 32 and a correct cytological diagnosis was made in 22 patients. Retrospective review of cytological material, taking into account the new specific features of squamoid metaplasia and infarction, improved this to 31 patients having cytological smears suggestive or diagnostic of adenolymphoma.

			%	95% CI
Definitive Report	Diagnostic of adenolymphoma	21/32	65·6%	0·47–0·81
	Diagnostic and suggestive results combined	24/32	75%*	0·57–0·89
Retrospective Report (AJW)	Diagnostic of adenolymphoma	25/32	78·1%	0·60–0·91
	Diagnostic and suggestive results combined	31/32	96·8%*	0·84–1·0

(*P=<0·05 McNemar test)

CE was performed in 12 patients and superficial parotidectomy in 11. Ten other operations were described. Of the three patients with postoperative facial nerve weakness and two with Frey's syndrome, none were related to CE. There were no tumour recurrences.

Conclusion: Squamoid metaplasia and infarction are well documented, though seemingly often ignored, features of parotid adenolymphoma. Attention to these aspects improves cytological diagnosis and allows better directed surgical management.

Percutaneous sclerotherapy of idiopathic varicocele in childhood. Review of 27 cases

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Management of left idiopathic varicocele in childhood is widely accepted to prevent testicular damage. Surgical techniques are often disappointing, with high recurrence rate in relation with anatomical variations (collateral and anastomosis).

Percutaneous sclerotherapy seems to offer better results (sclerosis of varicocele itself and control of run-off via collaterals).

During a period of four years, 27 patients aged nine to 16, with left sided idiopathic varicoceles, grade II or III according to classification of Dubin and Amelar, were treated by percutaneous retrograde sclerotherapy of the left internal spermatic vein.

Under local anesthesia and with fluoroscopic control, a co-axial catheter 5-F is introduced via the right femoral vein into the left renal vein (Seldinger method). 3 to 6 cc of sclerosing agent are injected into the testicular vein and its collaterals. After removal of the catheter, the patient is kept under observation for 3 hours.

No major complication was observed. Clinical and sonographic review occurred at 3, 6, 12 months. Follow-up ranged from 1 to 7 years (mean 34 months).

The sclerotherapy was performed in 26 boys (feasibility rate 96·3 per cent). Two boys showed persistent varicoceles at 3 months (persistent rate: 7·4 per cent) but repeat sclerotherapy was performed successfully. Three of four boys (75 per cent) with testicular volume loss demonstrated testicular catch-up growth in the first year of follow-up.

Finally, all varicoceles were occluded after one ($n=24$) or two ($n=2$) sessions.

In conclusion: Percutaneous sclerotherapy under local anesthesia proved to be an efficient and convenient treatment of varicocele in childhood.

Postoperative emergency attendance and hospital stay in day care coloproctological surgery

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The necessity to stay in hospital after an operation and to represent to the Emergency department on the following days are concerns in Day Surgery. During the first year of experience in our Unit of Major Day Surgery, these situations have been analysed in Coloproctologic Surgery, to study the causes and try to minimize them, also as a quality indicator of our activity.

Material/methods: A prospective follow-up of all patients operated in our unit has been designed. During the first year (October 1996–1997) we performed 379 coloproctological procedures distributed as follows: 133 haemorrhoidectomies, 75 fissures, 67 fistulas, 29 pilonidal sinus, 28 condylomas, 8 abscesses, 2 hidradenitis and 31 miscellanies.

A prospective follow-up of all the patients have been performed, and the results have been analysed.

Results: Four patients (1 per cent of the total) remained in hospital after surgery. One of them, a fistulectomy, because of bleeding. The other three (haemorrhoidal operations) because of excessive pain.

14 patients came to the Emergency Department on the days after surgery (37 per cent), most of them because of bleeding. For each procedure the frequencies of emergency visits were as follows: 6 hemorrhoidectomies (4·5 per cent), 5 fistulas (7 per cent), 2 abscesses (25 per cent), 1 condyloma (4 per cent) and 1 pilonidal sinus (3 per cent). No statistic significant differences were found in this distribution of frequencies, but the Logistic Regression Analysis shows a major relative risk (6 times higher; $P=0{\cdot}0475$) of Emergency attendance in abscesses and a statistical trend of major risk (around 1·4) in fistulas, compared to hemorrhoidal procedures.

Age and anesthetic procedure had no demonstrable influence in hospital stay after surgery nor in emergency attendance.

Conclusions: Between 2·11 per cent and 6·27 per cent of patients require emergency attendance after coloproctological day surgery ($P<0{\cdot}05$) for several reasons.

Between 0·52 per cent and 2·87 per cent ($P<0{\cdot}05$) of patients need to remain in hospital, mostly because of pain. The risk of requiring postoperative emergency attendance in abscess surgery is six times higher than in haemorrhoids.

The importance of a day-surgery unit in the organization of the activity of a specialistic surgical division

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Aim of the study: The availability of a day hospital facility with independent beds has allowed us to activate a day-surgery unit, according to the day ward model with dedicated theatre (RCS. Guidelines 1992). The aim was to treat intermediate pathologies with efficiency and effectiveness without slowing down the activity dedicated to complex cases.

Materials and methods: From March 1994 to December 1996, 814 interventions in day surgery have been performed. At the Day Surgery Unit of our institution (281 hernial tension-free repairs, 301 oncological surgical procedures and 224 proctology, phlebology, general surgery and urology interventions). The organisational protocol schedules a first day care selection visit, a day-hospital admission with two programmed visits [a) preoperative evaluation and b) the day of surgery] and a follow-up visit. 720 cases have been subjected to infiltration anesthesia with 1 per cent buffered Mepivacaine or Lidocaine. Spinal anesthesia has been mainly used for proctological and phlebological interventions in 63 cases, while a locoregional block (according to Winnie) has been performed in 25 cases.

Results: We observed 33 complications among 814 treated patients (4·1 per cent): hematomas, seromas and infection, these latter observed in less than 0·5 per cent of cases. One patient from 814 (0·1 per cent) has been submitted to general anaesthesia for intolerance of the treatment; seven patients have been converted from the treatment in the day hospital to ordinary hospitalization. The mean duration of hospital stay has been of 3·5 hours; with no significant differences between the different analysed groups. 97 per cent of patients have been totally satisfied by the experience, and 2·5 per cent partially satisfied. Only four patients have formulated a completely negative judgment, probably bound to bad or incomplete information about the procedure.

Conclusions: The high percentage of satisfaction and the low rate of complications show that the organizational model of day surgery is optimal to integrate the treatment of average complexity pathologies in the activity of a specialistic department.

Complicated varicose vein surgery in a Hungarian private day-case unit

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The aim of this study is to show that even complicated varicose vein surgery can safely be performed as day surgery in a country where this does not have a tradition.

Strict diagnostic and therapeutic protocol was followed. A continuous wave (CW) Doppler investigation was done in every case after physical examination and phlebography was performed for lesser saphenous vein (LSV) incompetence. Complications such as leg ulcers or superficial thrombophlebitis did not, but American Society of Anaesthesiologists (ASA) class 3 unstable or worse physical status did contraindicate day care surgery.

Between 1992 and 1997 551 extremities of 457 patients (99 men, 358 women) were operated on. The mean age was 45 years (range 17–83). At the time of surgery 35 patients (six per cent) had venous ulcer, 62 (11 per cent) had venous eczema or liposclerosis. Twenty-four procedures (4 per cent) were performed for acute varicophlebitis, out of them six had thrombi floating into the deep vein. The standard surgical procedure was high ligation of the greater saphenous vein (GSV, 496 extremities), LSV (32 extremities), or both (23 extremities), stripping and stab incision avulsion varicectomy. Surgery was performed under local anaesthesia, completed with sedatives. The standard hospital stay was 10 hours. Only two patients (0·36 per cent) had to be hospitalized for blood pressure disturbances for 24 hours. There was no need for hospitalization for surgery related complication. The only wound infection (0·18 per cent) was treated successfully on an outpatient basis.

Our results: total postoperative morbidity 0·9 per cent, ulcers healing within 8 weeks, no wound infection after surgery for venous ulcers, immediate pain relief in varicophlebitis, shows, that even complicated varicose vein surgery can be performed safely on an outpatient basis.

Audit of the value of a trauma team in a District General Hospital

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Aim of the study: To provide early appropriate assessment, resuscitation and intervention of patients following trauma with early referral for specialist treatment; to audit patient numbers, clinical performance and resource management together with continuing education of trauma care staff.
Materials and methods: Between January 1994 to June 1997 422 patients presented to Accident & Emergency necessitating callout of the defined trauma team (a representative of surgery, orthopaedics and anaesthetics). A more detailed audit involving 55 patients presenting over the latter six months of this audit showed that 46 (85 per cent) had a Revised Trauma Score (RTS) of 12. There were four seriously injured patients (RTS<10) one of whom died. Most patients presented with blunt trauma (road traffic accidents or falls); there were 3 patients who presented with penetrating injuries.
Summary of results: 32 patients (59 per cent) were seen by the complete trauma team within 5 minutes; all but one were seen within 20 minutes. All these data are submitted to the Major Trauma Outcomes Study (MTOS).
Conclusions: The volume of severe multiple injured patients is small but the trauma team call out system ensures early and complete triage but is demanding of resources. Further audit has shown that calls put out between 11pm–9am are as safe, relying on triage by Accident & Emergency staff alone during daytime hours.

Undetected pancreatic trauma in patients with severe abdominal trauma

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Study: Aim of the study is to evaluate undetected pancreatic complications (UPC) rates in patients operated for severe abdominal trauma (SAT), who had during the post-operative course (POC) symptoms of pancreatic trauma (PT) not demonstrated by pre-operative investigations and during laparotomy.
Materials and methods: 15 patients (12 males and 3 females) with a mean age of 37 years, who had, during the POC, complications related to undetected PT were retrospectively evaluated on the basis of laboratory findings, radiologic studies, early complications and surgical management.
Results: The UPC were hemorrhage in 6 patients (40 per cent), amylase elevations in 4 (26·6 per cent), intraabdominal collection in 2 (13·3 per cent), sepsis in 2 (13·3 per cent) and pancreatic fistula in 1 (6·6 per cent). 14 reinterventions were performed on 9 patients (60 per cent), while 6 (40 per cent) patients were treated conservatively. According to Lucas, the patients were grouped: 5 (33·3 per cent) grade 1; 4 (26·6 per cent) grade 2; 4 (26·6 per cent) grade 3; 2 (13·3 per cent) grade 4.

Complications and mortality rates in these series were respectively 80 per cent and 33 per cent during the second post-operative time.
Conclusions: Our experience shows the incapacity of laboratory findings and radiologic studies to evaluate correctly, during an emergency, pancreatic trauma in patients with SAT. We believe that in uncertain cases, monitoring of amylase and lypase levels in intra-abdominal fluids can help in the management of these critical patients.

Early post-operative diagnosis and early reoperation, in fact; can reduce complications and mortality rates.

The use of nerve supplied fasciocutaneous free flaps for covering soft tissue losses of the foot

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General approach: In order for a covering method of the foot's soft tissue losses to be chosen, the surgical team has to take into account the main role the foot has to play in maintaining the posture of the human body. Therefore the flaps chosen must be thick enough, well vascularized and, above all, well innervated. Therein one of the best methods is the use of microsurgical free transfers of nerve supplied radial fasciocutaneous flaps.
Material and method: In the last five years, in our Plastic and Reconstructive Surgery and Microsurgery Clinic from Cluj-Napoca, Romania, this method was used on 37 casualties (31 males and 6 females) aged between 7 and 69 years. 20 of the casualties were acute traumas and the other 17 were post-traumatic or postoperative sequels.

In all the cases a fasciocutaneous forearm free flap based on the vascular radial pedicle and the sensitive branch of the musculocutaneous nerve was used. As source of blood supply for the flaps, the tibial anterior vascular pedicle (in 19 situations) and the tibial posterior vascular pedicle (in 18 situations) was used.
Results: The immediate postoperative evolution was a very good one, including the full integration of the flaps in 35 situations. In the remaining 2 cases, the flaps failed because of venous thromboses.

As for the long term evolution, we have noticed: 1) a very good integration of the flaps; 2) very good and early re-achievement of sense in 32 of the cases, without any ulcerative lesions occurring; 3) in only three of the cases the mediocre re-achievement of sense of the flaps allowed minor ulcers to appear; this problem has been surgically treated and never appeared again.
Conclusions: 1) The use of nerve supplied flaps prevents ulcerative lesions from occurring. 2) If no postoperative complications occur, time and costs of treatment are considerably reduced and the social and professional rehabilitation of the patients is hastened and improved.

Pleuro-pulmonary injuries in thoracic trauma

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Aim: Thoracic trauma accounts for approximately 25 per cent of trauma deaths, are recorded at half of the deaths in the multiple injury patients. The aim of this study is to evaluate the results regarding the pleuro-pulmonary consequences in a specific emergency department.
Material and method: This study analysed a total of 374 patients with thoracic trauma either as a single injury or as a part of a multiple injured situations admitted at the Bucharest Emergency Hospital between January 1993–August 1994. Twenty-eight parameters were recorded and analysed.
Results: There was a sex ratio 5:1 (male prevalence). The most frequent parietal lesion was rib fracture. Haemothorax (mostly minimal) was the most frequent situation being recorded in 90 per cent of the cases while pneumothorax was found only in 30 per cent of the patients. Pulmonary injury was found in 32 per cent of the cases. Mediastinum was involved in only 1·8 per cent of the patients. In 10·7 per cent patients a flail chest was recorded. Surprisingly there was no firm correlation with the degree of acute respiratory insufficiency.
Conclusions: In multiple injured patients the most common association for thoracic trauma was with limb injuries (fractures), with head trauma, respectively with abdominal trauma. The thorax-head trauma association was also the highest in terms of mortality. In 11·3 per cent of the cases there were more than two regional injuries. Thoracic trauma either as singe injury or in association remains a crucial clinical item with yet suf-

ficient unresolved problems from which the most important remains the management of the respiratory insufficiency.

Antibiotic prophylaxis in penetrating trauma – a prospective, randomized comparison of a single- vs. multiple-dose regimen

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Aim: The aim of the study was to analyse whether a single shot antibiotic offers the same antiinfective efficacy as a multiple dose regimen in patients with penetrating trauma. Additionally, the total costs of the anti-infective treatment consisting of the purchase price, the costs of the administration of the medication and the costs of antibiotics given to treat an infection were calculated.

Methods: In the phase IV trial 206 consecutive patients admitted with penetrating trauma of thorax, abdomen or limbs were prospectively randomized to receive a single dose ceftriaxone 2 g (to be given upon admission) or thrice daily cefotixin 2 g for three days (starting upon admission). At admission, 14 per cent of all patients were assessed as having minor trauma, 60·1 per cent moderately severe and 25·9 per cent severe injuries. There were no differences between the treatment groups in respect of postoperative variables. The end point was infection occurring within 10 days. To be included, patients had to have penetrating injury to only one part of the body, reach the hospital within two hours of being injured and receive adequate surgery within 16 hours of being injured. Patients were excluded if it appeared likely that they would require mechanical ventilation for more than 24 hours. Prolonged mechanical ventilation carries the increased risk of pulmonary infection, which could prevent reliable evaluation of antibiotic prophylaxis. The same applies to open or grade II/III craniocerebral trauma. Randomization was stratified for abdomen, thorax and limbs. Statistical analysis was carried out using the SPSS/PC 5.0.2 statistics package, Testimate 5.1.1 and SAS for Windows 6.0. The frequency of infections up to the trial end point was analysed using the Santer CM test for 2×2 field tables. In addition, exploratory t-tests were carried out to obtain descriptive t-values.

Results: 11 patients withdrew from the trial, leaving 97 patients in the ceftriaxone group and 98 in the cefoxitin group. 96 per cent of the ceftriaxone group and 95 per cent of the cefoxitin group remained infection-free. In the ceftriaxone group, one patient developed a superficial infection, another showed clinical signs of infection that could not be localized, one patient developed a late superficial infection on day 20, and another developed superficial infection after reoperation. In the cefoxitin group two patients developed superficial infections, pneumonia was suspected clinically but not confirmed in one patient, and two others developed superficial infection after reoperation. In neither treatment group was deep infection, abscess, phlegmon or sepsis seen. No patient required additional surgery or intensive care due to infection. At $41·83 vs. $172·16, the average costs of delivering medication, including staff time, was significantly lower in the ceftriaxone group ($P<0{\cdot}001$).

Conclusion: When started early, antibiotic prophylaxis with a single 2 g dose of ceftriaxone on the day of injury or thrice daily 2 g cefoxitin for 3 days confers a high degree of protection against post-traumatic infection. Prophylaxis with a single dose of ceftriaxone has considerable practical and economic advantages.

Antibiotic prophylaxis of traumatic lacerations in limb injuries

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Aim of the study: The need for antimicrobial prophylaxis was examined in 100 patients, with minor limb injury wounds presenting in Astros Health Center.

Materials and methods: 100 patients, 78 males (78 per cent) and 22 females (22 per cent) were prospectively randomized to one of two treatment groups. Patients in group A (n=52) received antibiotic prophylaxis, with 625 mg amoxycillin plus 125 mg clavulanate administered orally, in 3 daily doses, for 4 days. In patients assigned in group B (n=48), no antibiotics were given. All wounds underwent a standard surgical toilet and then were closed under aseptic conditions. Patients' wounds were re-examined for wound inflammation and presence of pus, between 5 and 10 days after suture.

Results: The mean age of patients was 47 years (range: 12–66 years). Patients of both groups did not differ significantly in parameters like gender, age, cause of injury, trauma length, depth and pattern, placement of deep sutures, surgical debridement, as well as factors adversely affecting wound healing, like diabetes mellitus, cancer, use of immunosuppressive agents or corticosteroids. Six patients (12·5 per cent) in group A and 10 patients (20·8 per cent) in group B suffered a wound infection. This difference was found to be statistically non-significant ($P>0{\cdot}10$).

Conclusions: In our study antimicrobial prophylaxis did not reduce wound infection rate in minor limb injury wounds. Routine antibiotic prophylaxis in minor limb injury wounds is discouraged.

Retroperitoneoscopic adrenalectomy from a posterior approach

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A number of conventional techniques are available for adrenalectomy. The rapid development of minimal invasive surgery has reached the adrenal area. The technique of endoscopic retroperitoneal adrenalectomy elaborated in 1995, has not yet become widespread. Our initial experience with retroperitoneoscopic adrenalectomy is described.

Patients and methods: A 32- and a 28-year-old women, both with primary adrenal gland tumours require unilateral adrenalectomy. One of the patients had a phaeochromocytoma, while the other patient had Cushing's syndrome due to an adrenal adenoma. Both tumours were on the left side. The patient with the phaeochromocytoma was prepared with phenoxybenzamine and propranolol. The same operative technique was used as that described by Waltz. The operations were performed under general anesthesia in the prone position. A 1·5 cm skin incision was made just below the tip of the 12th rib. A smaller retroperitoneal cavity under the dorsolumbar fascia was created by blunt digital dissection. Under internal finger guidance, 5 cm laterally a 5 mm trocar and 5 cm medially a 12 mm trocar were inserted. Into the initial incision site, a blunt 10 mm trocar with an inflatable balloon was introduced. Following carbon dioxide insufflation at a pressure of 15–20 mm Hg, the kidney was visualized and the adrenal gland approached near the anteromedial border of the kidney. The gland was dissected and the vessels were divided with an ultrasonically activated scalpel (Harmonic Scalpel, UltraCision, Smithfield, RI). The completely mobilized adrenal gland tumours (2·5 and 5 cm diameter) were removed within an endopouch.

Results: Both procedures were successfully completed. The operating time were 150 and 90 minutes, blood loss was minimal (20–50 ml). There were no intraoperative or postoperative complications. The duration of postoperative hospitalization in both cases was 3 days. Histological examination confirmed the preoperative diagnosis (no evidence of malignancy and complete excision).

Conclusion: Retroperitoneoscopic adrenalectomy is safe and involves less pain and permits a rapid return to normal activity. It may be a preferred method for removing medium-sized (up to 5 cm) unilateral lesions of the adrenal gland.

Impact of diagnostic laparoscopy on the management of acute abdominal pain in young women

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Aim: Acute appendicitis accounts for less than 40 per cent[1] of presentations of acute abdominal pain in young women. Non-invasive studies are frequently employed to determine other causes of acute abdominal pain in patients treated conservatively. The aim of this study is to evaluate the impact of diagnostic laparoscopy in the management of acute abdominal pain in women less than 30 years of age.

Method: A total cohort of 130 patients (1991–1997) were included with a mean age of 21·5 years.

Results: At laparoscopy, the diagnosis of acute appendicitis was made in 62 patients (48 per cent). Histology confirmed this diagnosis in 58 (94 per cent). An additional 16 visually normal appendices were removed, six of which contained histologic abnormalities (four acutely inflamed, two fibrosis/obliterated lumen).

Gynaecological causes of pain were found in 37 patients (28 per cent). These included 33 cases of ovarian cysts, 1 infarcted ovary, 1 case of endometriosis and 2 cases of pelvic inflammatory disease. Seven patients had miscellaneous diagnoses and no cause was found in the remaining 8 patients.

Conclusion: Diagnostic laparoscopy is a useful modality in the evaluation of acute abdominal pain in young women. Positive findings may be expected in the majority of patients. Our findings suggest that negative appendicectomies may be reduced using this method.

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[1] *Br. J. Surg* vol 76(11) pp. 1121–1125, 1989.

Adjustable minimally invasive surgery applicator (AMISA) for tissue management

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Aim: In thoracoscopy and laparoscopy the options for tissue management can be greatly expanded by the use of a collagen bandage coated with components of fibrin glue. This biodegradable tool has proven to be of particular value, and even leads to interesting extensions of indications.

Methods: In experimental surface models the different methods of liquid gluing proved to be fairly unstable, therefore an adjustable MIS applicator (AMISA) for the patch-bound glue was developed which simplified the introduction and placing of the 10×5 cm collagen bandage coated with tissue glue in the appropriate body cavity. Because of the application of such a large patch, not only haemostasis, but also rapid sealing of larger tissue defects in the pleural and abdominal cavities was made possible. To demonstrate the surface stabilizing properties of liquid glues and patch-bound glues, a simulation model with a pressure chamber was built. The pressure at the upper limit was measured. A ready-to-use product of a collagen bandage coated with components of tissue glue was optimal as regards its sealing and gluing properties.

Results: If the experimental results are applied to surgical practice (1994–1997), the selective leak closure (SLC) of the visceral pleura could be used to treat diseases of the pleura and diseases of the pulmonary structures. Pleural leaks, of which 83 were pneumothorax and 11 chylothorax have been treated successfully, in hepatic, biliary, and splenic surgery the collagen bandage was used as a sealant in resections (26), Hodgkin staging (7), closure of biliary fistulas (5) and MIS-management in blunt abdominal trauma (17).

Conclusions: The innovative MIS-application of bandage-bound tissue glue in addition to increasing the number of potential indications, also expanded existing indications. The following endpoints can be defined: increase in the effectiveness of the selected procedure (reduction of draining time), increase in the efficiency (reduction of complications), decrease in intensive care, improvement in psychosocial structure (decrease in hospitalization, improved parent–child relationships).

Short term comparison of laparoscopic antireflux surgery to conservative therapy for reflux oesophagitis

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The present study evaluates short term symptomatic and endoscopic outcome in gastroesophageal reflux disease comparing conservative therapy to operative management.

The study comprised 110 consecutive patients referred for reflux syndromes and erosive gastritis confirmed by endoscopy from 1993 to 1994. The patients received conservative management and medication. The oesophageal healing was evaluated by endoscopy. If conservative management failed to relieve symptoms and esophageal healing, laparoscopic antireflux surgery was performed. The patients were followed-up by clinical examinations and interviews/median 4·74 years.

Laparoscopic antireflux surgery was performed in 35 of 110 patients. Results at their follow-up: 32 (91 per cent) had no heartburn, 31 (89 per cent) were free from erosive gastritis, only 1 (3 per cent) was given medication. Corresponding figures in conservative group was 56 (75 per cent), 49 (65 per cent), 16 (21 per cent).

In gastroesophageal reflux disease the laparoscopic surgical treatment gave much more favourable short term results compared to those from conservative therapy.

The safety of laparoscopic cholecystectomy in sickle cell disease

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Aim: Patients with sickle cell disease (SCD) are at an increased risk of developing pigmented gall stones which require surgical intervention. However, surgery is associated with high morbidity and mortality. Minimally invasive surgery offers an attractive option due to its numerous advantages over the conventional methods.

Materials and methods: From October 1992–December 1996, 71 SCD patients (42 males, 29 females) with gall stones underwent laparoscopic cholecystectomy (LC) which was done electively in 65 patients. Their mean age was 25 (range 13–58) years. 47 patients have had sickle crises ranging 1–10 per year. The symptoms were: upper abdominal pain (65), fatty food intolerance (33), nausea & vomiting (56) and jaundice (12). Five patients were asymptomatic. The mean preoperative haemoglobin was 9 (range 6·3–13·5) g/dl and mean HbF and HbS were 14·5 per cent (range 6·6–33) and 72·4 per cent (range 54–90·9), respectively. Preoperatively, 42 patients received simple blood transfusion (group 1), 13 were given exchange transfusion (group 2) and 16 had no transfusion (group 3).

Results: The mean operative time was 80 (range 40–270) min. Four cases (5·6 per cent) were converted to open. Ten patients (nine from group 1 and one from group 3) developed complications: acute chest syndrome 2, atelectasis 2, chest infections 2, wound infections 2, vasoocclusive crisis 1 and abdominal wall haematoma 1. There was one mortality (group 3) due to vasoocclusive crisis. The median hospital stay was 2·5 (range 1–10) days.

Conclusion: LC can be conducted safely in patients with SCD. Preoperative exchange transfusion is advocated in sickle patients undergoing surgery as it is associated with less morbidity and mortality, but this needs further evaluation.

The effect of total parenteral nutrition on immunological system

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It has been reported that immunosuppression is induced with long lasting administration of total parenteral nutrition (TPN). However, the present clinical status of the patient may be another parameter to affect this situation.
Aim: To investigate the effect of TPN on the immune system of patients unable to feed orally.
Materials and methods: In this study, the effect of TPN on the immunological states of 20 patients who had no oral intake at least for five days were investigated in a randomized fashion. The patients who had received radiotherapy or chemotherapy and who were immune compromized were excluded from the study. T-lymphocyte (CD3+), B-lymphocyte (CD19+) and total lymphocyte (CD45+) counts, and IgG, IgM and IgA levels were measured at the beginning, at the 5th and 10th days of TPN. The immunological changes were compared with ANOVA test.
Results: The mean levels of IgG, IgM and IgA before TPN were 915·50 mg/dl, 107·15 mg/dl and 201·05 mg/dl, respectively. The mean initial counts of CD3+, CD19+ and CD45+ were 57·96 10^9/l, 34·96 10^9/l and 88·94 10^9/l, respectively. In the 5th day of TPN, the mean levels were measured as IgG 985·91 mg/dl, IgM 106·10 mg/dl, IgA 207·05 mg/dl, CD3+ 58·63 10^9/l, CD19+ 24·52 10^9/l and CD45+ 87·95 10^9/l. In the 10th day of TPN, the mean levels were measured as IgG 1102·8 mg/dl, IgM 128·90 mg/dl, IgA 209·22 mg/dl, CD3+ 66·82 10^9/l, CD19+ 28·96 10^9/l and CD45+ 87·51 10^9/l. There was an insignificant increase of IgG, IgA, IgM and CD3+ levels and an insignificant decrease of CD19+ level at the end of TPN when compared to the beginning of TPN (P>0·05), while there was no change in the levels of CD45+.
Conclusions: Contrary to conventional knowledge, TPN does not affect the immunological parameters negatively apart from a decrease in the levels of CD19+.

Malignant peritoneal mesothelioma following abdominal radiotherapy

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Malignant peritoneal mesothelioma MPM is a rare aggressive and highly malignant neoplasm. It is usually derived from the mesothelial lining of the peritoneal cavity and well documented to follow a long period of exposure to asbestos. It was also found to happen after radiation exposure. Previous reported cases of MPM classical presentation were four cases of malignant mesothelioma following treatment of Hodgkin's disease with radiotherapy.

Here we add two cases of primary malignant mesothelioma occurring many years after treating testicular neoplasm with abdominal radiotherapy and without any known history or clinical evidence of previous exposure to asbestos. Both patients were men fifty-five and sixty-four years old. Abdominal malignant mesothelioma had followed abdominal radiotherapy, which was given for testicular tumours (17–35) years before presentation. To establish the final diagnosis after excluding the other possibilities, malignant mesothelioma it is essential to remember as a possible cause of such rare abdominal lesion. Although our methods of obtaining tissue samples for histological confirmation were the explorative laparotomy. CT scan guided multiple fine needle aspirations could be a useful tool to achieve the same goal. Further staining of the tumour specimens immunohistochemically in addition to the haematoxylin-eosin staining was also done for additional confirmation. Tumour cells positively for CA125, epithelial membrane antigen and negativity for CEA are characteristic of malignant mesothelioma. All these variety of investigation are required to refute the possible peritoneal metastasis from a primary gastrointestinal adenocarcinomas.

In conclusion MPM may occur after long period of previous radiotherapy and may need to be considered in the list of possible diagnosis of peritoneal malignancy.

A prospective, randomized trial of early enteral feeding after resection for colorectal cancer

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The purpose of the study was to determine whether early postoperative enteral feeding decreased mortality and morbidity in patients with colorectal cancer. Between January 1996 to September 1997, 65 patients with a resectable colorectal cancer were randomized to enteral feeding via jejunostomy tube (EEF) or control (CNTL). There were 41 male and 24 female with an overall mean age of 69·4 years. The table shows the site of colorectal cancer.

Site	EEF (No. of patients)	CNTL (No. of patients)
Right colon	8 (25·8%)	8 (23·5%)
Transverse colon	2 (6·5%)	2 (5·8%)
Left colon	13 (41·9%)	15 (44·1%)
Rectum	8 (25·8%)	9 (26·6%)
Total (65 patients)	31	34

Tube feeding was begun on the first postoperative day and advanced to a goal of 25 Kcal/kg per day. The CNTL were given intravenous crystalloid solutions. Patient preoperative status by nutrition risk index (NRI) and operative factors were similar between the groups. The results in terms of postoperative incidence of mortality and morbidity, and NRI decrease (from low-medium risk group to high risk group) between the groups were analysed by chi square test.

One patient in the EEF group had the jejunostomy tube dislocated in the abdomen cavity, required reoperation and was excluded from the study. The table shows the incidence of postoperative complication.

Complications	EEF	CNTL
Death	2 (6·4%)	2 (5·8%)
Sepsis	4 (12·9%)	6 (17·6%)
Nausea	6 (19·3%)	3 (8·8%)
Diarrhoea	1 (3·2%)	0

There was no significant difference in number of postoperative complications between the groups. There was no significant difference in postoperative NRI decrease between the groups (EEF vs CNTL 5/16 & vs 4/14 P=n.s.).

Early enteral feeding via jejunostomy was not beneficial in the postoperative treatment of colorectal resected cancer.

Learn operative surgery on a computer first

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As an educational ideal, the surgical trainee should be so well instructed that he or she will be an expert in an operation before performing it for the first time. Traditional methods of surgical training fall short of this ideal, concentrating on the principles of the operation supported by learning on the job. This paper aims to demonstrate how training in operative surgery can move from apprenticeship towards preoperative expertise using computer based learning.

Two of our CD-ROMs, on Laparoscopic Cholecystectomy and Basic Surgical Skills, are the basis of the paper. We can demonstrate live at the Congress, given computer projection facilities, the many aspects of this work.

We have developed a new surgical language to allow virtually unlimited operative text in an accessible form for the trainee.

Multimedia features include the written word, diagrams, photographs, animations, video runs and a choice of voice to suit national preferences.

Interactive features include learning ability profiling; aptitude testing;

text annotation; customizing of equipment, materials, patient information, and nursing care plans; control of videos; dissection simulators; surgical decision simulators; drug dose calculators; surgical skidpans to let trainees test materials to destruction; speed and accuracy trials; and testing of trainees, with progress advice. A validation study is in progress.

We suggest that this type of computer based learning is an important and fast-developing method of making trainees competent before they start operating on patients.

New classification for ultrasonic carotid plaque morphology

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Aim: To provide new operator independent classification of ultrasonic carotid plaque morphology.

Methods: 100 plaques (32 symptomatic, 68 asymptomatic; producing more than 50 per cent stenosis) were randomly selected. B-mode images were transferred to computer. Image standardization was performed so that adventitia and blood would have a grey value of 190 and 0 respectively (grey scale 0 = black; 255 = white). Plaques were outlined and the histogram of grey levels of the pixels was obtained. The median value of the grey scale level of pixels (GSM) was taken as a measure of overall echolucency (GSM <40 = echolucent; GSM >40 == echogenic). Kurtosis of the histogram was taken as an index of overall heterogeneity (<3 = heterogeneous and >3 = homogenous).

Results: A high incidence of symptomatic plaques (13/19; 41 per cent) was associated with a GSM <40 and a leptokurtosis (>3), compared to an incidence of 25 per cent (8/24; P=0·002 wilcoxon test). A GSM >40 and platykurtosis were associated with 33 per cent incidence of symptomatic plaques. The mean diameter stenosis was not significantly different among the three different groups (P=0·2, Wilcoxon test). Echolucent and homogenous texture are more likely to be associated with hemispheric symptoms.

Conclusion: Computer assisted methods identified a subgroup of patients at higher risk. This should be tested in future prospective CEA trials with stroke as an end point.

Vacuum sealing: a new and promising regimen in the therapy of radiation ulcers

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Treatment of chronic radiation ulcers of any localization represents still a major challenge in surgery. These lesions develop on the basis of vascular malperfusion and chronic infection. Surgical intervention requires wound coverage by local flaps well described in the literature. Preoperative wound conditioning however is still a problem.

Established conservative methods of wound preconditioning are primary excision of the ulcers including bony lesions and induction of granulation by different means. The major concern about this strategy however is the cost intensity due to the duration of the treatment and costs for wound dressings, potential drugs etc.

Here we present an innovative wound dressing technique as an alternative treatment for radiation ulcers.

The treatment includes the following regimen. After wound excision and subsequent placement of polyvinylalcoholic (PVA) sponges wounds are continuously drained by draining tubes inserted into the sponge matrix. Next, the lesions are vacuum sealed by transparent vapour-permeable polyurethane foils. Finally, standard vacuum drainage containers, loaded with up to 80 kPa subatmospheric pressure, are connected to the tubes. Wound dressings have to be changed only every 7 days.

In this paper the advantages of wound dressing based on vacuum sealing in preoperative wound conditioning of radiation ulcers will be demonstrated by case reports.

The advantages of the specified technique are: 1) Reduction of the time required to clean the wound and earlier formation of granulation tissue by subatmospheric pressure thus enabling earlier operation. 2) Improved hygiene since the system represents a so-called closed system. 3) Reduction in material and personal costs.

In conclusion we consider vacuum sealing in the management of chronic radiation ulcers as an excellent alternative in wound preconditioning.

Hospital management, the surgeon as 'economist'

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Considering the legal conditions there is no question that with the Health Structure Act (GSG) changes in hospital infrastructure have to be made by the surgeon and the administration cojointly. Contracts between hospitals and health insurances are covering costs for inpatient and outpatient surgical treatment. New forms of payment fee, either for case (Fallpauschale) or for service (Sonderentgelt) and a fixed budget for the hospital by the health insurances have been introduced.

Based on the establishment of an efficient computer software (Medwork) and hardware equipment (network with 25 single user workstations) all data for medical treatment in the surgical department are collected. The conversion of diagnoses and therapies to ICD-10/ICPM numbers is possible. By analysing the data and statistical evaluation 'controlling' is a major task for the physician in order for hospital decisions, cost containment and the use of cost effectiveness analysis.

Economical aspects and quality control of medical services, hospital budgets and finally planning capacity for hospital care are the new challenges for the surgeon.

From our experience an efficient budget control needs a complete and correct data recording – employing an efficient software – as well as strict medical control of profits along with continuous communication between the surgeons themselves and with the administration.

Cellular activity in human peritoneum after laparoscopic and conventional operations and in peritonitis

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Aim of the study: The peritoneal trauma is reflected by an ill-defined influence on the patient's homeostasis. We therefore investigated immunohistochemically the local peritoneal response to different surgical procedures and peritonitis.

Materials and methods: In 10 patients, with laparoscopic or conventional cholecystectomy, peritoneal specimens were taken from the incision or parietal resection margins at the beginning and at the end of the intervention. In nine patients with diffuse peritonitis specimens were taken at the beginning of the intervention. Monocyte/-macrophage activity was assessed immunohistochemically using the antibody clone HAM 56 for local macrophages and antibodies against macrophages inhibiting factor (MIF)-related proteins 8 and 14 (MRP 8 and 14). Antibacterial protein (Defensin 3) reflected the activation of granulocytes. Cellular expression of interleukin 1 (IL-1), interleukin 6 (IL-6) and intercellular adhesion molecule-1 (ICAM-1) was additionally measured. All examinations were performed in paraffin sections using the Avitin-Biotin-Complex-technique.

Summary of results: Cellular activation (MRP 8 and 14, Defensin 3) as well as expression of adhesion molecules (ICAM-1) were increased in patients with either laparoscopic or conventional cholecystectomy. In peritonitis the expression of MRP 8 and 14 showed a focally increased interstitial staining whereas HAM 56 showed a relatively slight increase. The IL-1 expression in these patients was only discrete and in some cases not detectable.

Conclusions: The immunohistochemical evaluation of the local cellular response may provide objective criteria for the grading of the peritoneal trauma. Peritoneal response to laparoscopic or conventional cholecystectomy showed a comparable activation pattern. In peritonitis the peritoneal inflammatory reaction is relatively uniform. The surprisingly low expression of IL-1 may reflect downregulation after supposed early increase during the course of peritonitis.

Results after surgical treatment for pelvic floor disease in adult patients

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To date no specific single ideal surgical treatment has been identified for pelvic floor disease including rectal prolapse, rectocoele, cystocoele, vault prolapse or a combination. The pathophysiology and controversies surrounding continence and constipation remain topics of debate. The present study summarizes our single center experience according to functional improvement after surgery.

Patients and methods: From February 1993 till November 1996 16 patients (1M, 15F) were treated for pelvic floor disease in our department, ranging in age from 34 to 75 years (mean 59 years). Initial disease was rectal prolapse in six patients, two in combination with rectal ulcers by intussusception, two patients with both rectocoele and prolapse, three patients with rectocoele, four with recto- and cystocoele and one patient with vault prolapse.

A detailed history was obtained from each patient both pre- and postoperatively, including functional symptoms as rectal dyschezia, faecal and urinary incontinence, anal manometry, constipation and recurrent prolapse. Surgical treatment consisted of rectopexy in six patients, in three combined with partial sigmoidectomy and 10 patients had a posterior colporaphy. Defecography and anal manometry was performed in all patients. Postoperative follow-up was 32 months (range 12–50 months).

Results: During follow-up none of the patients developed a recurrence of complete prolapse of rectum or vault. Faecal incontinence was still present in one of six patients (16·6 per cent) who had complaints before surgery. Rectal dyschezia is present in two patients of 10 (20 per cent), urinary incontinence was absent in all patients after treatment (0/4). Constipation was pre-operatively seen in 15 of 16 patients, while after surgery no problems occurred in all patients. Six patients however had to use medication. Post-operatively no insufficiency of the pelvic floor musculature was seen with anal manometry.

Conclusion: The present study demonstrated that the risk of developing recurrence of the symptoms after surgical treatment is rather small. Surgery therefore is a valid option in the treatment of these conditions with only minimal mid-term morbidity.

Giant retroperitoneal tumour: myxoid liposarcoma

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Introduction: Retroperitoneal tumours emerge from connective, nervous and embryonal structures situated in the retroperitoneal space and separate from the kidney, the suprarenal glands and the large vessels.

Liposarcoma is an uncommon tumour of mesodermic origin. It presents an histologically heterogeneous structure with some differentiated lipomatous type regions and others constituted by lopoblasts (irregularly shaped cells).

These tumours have a slow development and frequently reach a large size, which makes compressive symptoms the condition's most common manifestation. Growth is primarily local with little tendency to metastasize.

Material and method: A case of giant retroperitoneal tumour is presented. The symptoms and investigations are as follows: abdominal ultrasonography demonstrated a solid and hyperechogenic, large abdominal mass occupying the pelvis and right hemiabdomen. Abdominal CAT: heterogeneous retroperitoneal mass of a predominantly fatty nature causing migration of abdominal viscera. IV urogram: both kidneys shifted to the left mimicking cross-over ectopia. Echoguided puncture biopsy: cytology compatible with sarcoma.

Results: Surgery was done by block removal of the tumour. Dimensions of surgical piece removed were 40×40×14 cm, weight 13 730 kg.

Pathoanatomical diagnosis was a well differentiated liposarcoma with areas of myxoid liposarcoma.

Conclusions: Surgical resection of the tumour in a block is the choice treatment. Chemotherapy whether alone or associated with radiotherapy does not appear to obtain good results due to the low radiosensitivity of these conditions.

Effects of thyroid hormones on stress ulcer: an experimental study

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Aim of the study: Some non-thyroid diseases which cause stress, influence the serum thyroid hormone levels. It has been shown that there is a correlation between the severity of the gastric mucosal erosions and the decrease in thyroid hormone levels, in stress. We evaluated the possible protective effect of thyroid hormones on gastric mucosal lesions in a rat stress model.

Materials and methods: Stress (24 hours of hunger and six hours of stretch in supine position) was applied to five groups of rats, each of which contains 15 rats. Group I was the control group. Thyroxine (T4) was injected intramuscularly to the rats in the group II and III, and Triiodoythyronin (T3) was given intraperitoneally to the group IV and V. The thyroid hormone injections were made before the stress in groups II and IV, and during the stress in groups III and V.

After death blood samples were taken for thyroid hormone levels. Gastric pH of each rat was measured, gastric mucosal lesions were evaluated and histopathological examinations were performed.

Summary of results: It was found that gastric mucosal lesions were decreased in length and depth by thyroid hormones in all of the four treatment groups compared with the control group ($P<0 \cdot 001$). However, gastric pH levels were about the same with the control group. T3 levels were found to be elevated in group II, in which T4 was given during stress.

Conclusions: We conclude that thyroid hormones protect the gastric mucosa in both prophylactic and therapeutic usage. This result indirectly reveals that there becomes no decrease in 5'-deiodinase enzyme activity in stress.

Sugiura procedure in the treatment of bleeding esophageal varices

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Aim of the study: The aim of this study is to report our results and to make an attempt to define the possible role of the Sugiura procedure in the treatment of variceal bleeding.

Materials and methods: From January 1979 to December 1997, 39 patients with portal hypertension and acute variceal bleeding (17 patients) or with previous variceal bleeding (23 patients) underwent a Sugiura procedure. Operations were performed in two stages. When performed in an emergency situation (17 patients) the thoracic operation was performed first. In elective cases (23 patients) the more laborious and risky abdominal operation was preferred. The second stage, either abdominal or thoracic procedure, respectively was performed 4 weeks to 6 months later. A complete two-stage operation was performed in 16 patients. 23 patients did not undergo the second stage because of early postoperative death, deterioration of condition or refusal. There were 17 men and 22 women, aged 41·7±18·3 years (range 8–71 years). 27 patients (69 per cent) had cirrhosis. Three patients had noncirrhotic intrahepatic portal hypertension and nine patients had extrahepatic portal or splenic vein thrombosis. According to the Child–Turcotte classification of hepatic function there were 23 Child class A, 13 Child class B and 3 Child class C patients.

Summary of results: Overall operative mortality was 7·4 per cent (four out of 54 operations), mortality cases in emergency situation 17·6 per cent (three out of 17 operations) and in elective cases 2·7 per cent (three out

of 38 operations) Variceal rebleeding occurred in four survivors (11·4 per cent) at an average follow up of 6·1±4·3 years. Survival rate was 84·6 per cent at 1 year, 71·8 per cent at 5 years and 64·1 per cent at 10 years.
Conclusions: Sugiura operation carries low operative risk in an elective situation and results in an effective prevention of recurrent variceal bleeding.

Giant haemangiopericytoma

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Haemangiopericytoma is an unusual vascular tumour, that arises from the pericapillary pericyte cells of Zimmermann. It was described by Stout and Murray in 1942; and 25 per cent arise from the retroperitoneum and pelvic cavity.

A 46 year old male, came to the emergency room because of pain and oedema in the left lower extremity. On physical examination the abdomen appeared globular, and had one big intraabdominal mass. Signs of deep venous thrombosis were present. Blood studies were normal (include tumoral markers). We performed several X-rays examination: plain abdominal, pylography, ultrasonography, CT-scan, angiography, duplex-scan. We founded a soft tissue mass in the mesentery and pelvic cavity, with displacement of the bowel, bladder and the ureters The mass had cystic low attenuation zones and enhancement of solid areas with calcifications.

On the laparotomy we founded a giant and hypervascular mass, located in the mesosigmoid and pelvic cavity. The patient underwent complete excision of the tumour with sigmoidectomy and ureteral liberation End to end colorectal anastomosis was carried out. In the postoperative period the patient developed a urinary fistula, which was treated conservatively with drainage.

Pathology revealed a large tumour (30×25×22 cm), pseudoencapsulated and weighing 3560 g Microscopically the tumour showed small cells, with oval nuclei. The vascular channels usually formed a continuous ramifying vascular network or a 'staghorn' configuration. Few mitotic figures (One per 10 high power fields). Immunohistochemical stain for vimentin and CD 34 were positive The diagnosis was a 'low grade malignant hemangiopericytoma' The cytology of peritoneal fluid was negative
Conclusions: Big size and weight of the tumour The first symptom was a venous thrombosis Intratumoral calcification (less than 1 per cent of the cases). Sigmoid and ureters encapsulated.

Follow-up later one year is normal.

The mechanism of leg ulcer healing under the influence of the He-Ne laser irradiation

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Planimetric assessment of the healing process of diabetic leg ulcers proved that granulation and epithelization rate in diabetic neuropathy is 2–8 times more effective than in ischaemic ulcers (venous, arterial) This study was performed to show a mechanism of stimulation by He-Ne laser irradiation on cells of granulation tissue of these ulcers Activity of superoxydysmutase (SOD) was assessed in homogenated granulation tissue removed from ulcers due to overgrowth – before and after irradiation Simultaneously concentration of linked diens and malonic dialdehyd (MDA) as products of lipid's peroxydation was measured. He-Ne laser irradiation causes significantly higher activity of SOD and at the 4th day of therapy also significantly decreased concentration of linked diens and MDA. Stimulated by He-Ne lasers superoxydysmutase reduced peroxydation of intracellular lipids in human granulation tissue. This study is the first in human pathology

Biliary complications after orthotopic liver transplantation: influence of graft shipment?

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Stenoses at the anastomotic site, biliary obstruction, leakage and infections occur both in the immediate postoperative phase and even several years after orthotopic liver transplantation (OLT) and are frequently the cause of reoperation. The influence of organ preservation, including flushing of the bile duct, by a team of surgeons other than transplant surgeons is investigated in this study, together with the etiology of the biliary complications itself.

Patients and methods: From May 1991 till May 1997 210 OLT were performed in our institution in 167 adults and 43 children. 180 primary transplants were included in this study, 27 retransplantations and three patients included were second retransplants. Preoperatively donor status, shipment of the graft, flushing of bile ducts at the time of preservation and recipient age were studied, while after transplantation type of biliary anastomosis, postoperative biliary complications and patient and graft survival were observed. For statistical analysis Kaplan Maier-method was used.

Results: 70 transplantations were performed using a shipped donor liver, in four cases (5·7 per cent) the bile duct was not flushed at the time of preservation. Liver disease without involvement of the extrahepatic biliary tract was diagnosed in 186 transplants (88·6 per cent) (58 shipped, 128 non-shipped), while 24 patients (11.4 per cent) had involvement of the extrahepatic biliary tract (12 shipped, 12 non-shipped). 148 patients had an end-to-end anastomosis of the common bile ducts, 58 patients had a choledochojejunostomy and in four patients a choledochocystostomy was performed. A **T**-tube was placed in 83 patients (39·5 per cent). Postoperative biliary complications were seen in 21 (10 per cent) patients (nine shipped (12·8 per cent), 12 non shipped (8·6 per cent, P=n.s.) while one patient of four (25 per cent) where the bile duct was not flushed in the shipped group had biliary leakage (P=0·02). 10 patients had peritonitis because of biliary leakage (4·3 per cent), two patients with peritonitis because of a biliary fistula and perforation of the Roux-en-**Y** respectively. Seven patients (three children, four adults) had biliary obstruction, due to stenosis of the anastomosis (n=3), necrosis of the bile ducts (n=1), haemobilia (n=1), choledocholithiasis (n=1) and recurrent auto-immune hepatitis (n=1). One patient was reoperated because of an obstructed **T**-tube and one because of biliary sludge. No mortality because of biliary complications occurred with graft survival after 3, 6 and 12 months of 86·6 per cent, 79·4 per cent and 70·4 per cent respectively. Patient survival at the same time was 94·3 per cent, 91·2 per cent and 87·9 per cent.

Conclusion: Liver transplantation has reached a high technical standard, the biliary reconstruction frequently may complicate the postoperative recovery. Although the reported incidence for biliary complications is up to 20 per cent in literature, no increased mortality in these patients can be seen. Shipping of liver grafts may cause these complications in particular when flushing of the bile duct is not adequately performed.

Vascular complications (VCs) after renal transplantation

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VCs are the reason for 16·5 per cent of deaths and 12·5 per cent of haemodialyses because of delayed graft function after renal transplantations. VCs can be divided into arterial venous, connected with lymph leak as well as early and late.

The analysis of 339 patients with grafts harvested from cadaveric donors operated on in our Department from 1990 to 1997 was performed. Early arterial complications (up to three weeks after surgical procedure) – such as bleeding from: arterial anostomosis, small vessels of the kidney hilium and retroperitoneal space or ruptured kidney during rejection, occurred in 46 cases (13·6 per cent), and graft or lower limb ischaemia occurred in 18 (5·3 per cent). Early venous complications such as renal or iliac vein thrombosis occurred in three cases (0·9 per cent).

There were 65 (19·2 per cent) late arterial complications including six arterial anostomosis strictures giving signs of hypertension, five ischaemic ureteric strictures and 54 cases (15·9 per cent) of late renal artery and vein thrombosis caused by chronic rejection, three cases of impaired drainage of lymph from the graft area after surgical procedure were included as VCs as well.

VCs were the reason for recipient death in six cases and of graft loss in 54 (15·9 per cent). Most of the VCs are connected with the processes of acute rejection (graft rupture) and chronic rejection (arterial and venous thrombosis). Late graft ischemia is caused by atherosclerosis or endothelial proliferation in the site of anastomosis.

Liver transplantation in patients with cirrhosis and primary cellular hepatocarcinoma. How useful is the tumour staging?

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Background: Because of the effectiveness of liver transplantation, some aspects of the treatment of patients with liver cirrhosis have become challenging topics. One of these is the staging accuracy for the hepatocellular carcinoma (HCC) in the cirrhotic liver, in order to provide an adequate indication for the definitive treatment.

Aim of the study: To evaluate the diagnostic accuracy of HCC in cirrhosis using the clinical methods nowadays available.

Patients and methods: In our Institution, from November 1990 to January 1998, 202 orthotopic liver transplantations (OLT) with a piggyback modified technique were performed in 183 patients with end stage liver disorders. Diagnoses was made preoperatively by biological probes (alpha-fetoprotein), image methods as ultrasonography, magnetic resonance imaging, computerized tomography (CT), CT portography, lipiodol CT and hepatic angiography and also percutaneous needle biopsies of the suspicious images.

Results: In 33 patients, HCC diagnoses was made (32 with liver cirrhosis). The other 150 were considered to be free of HCC. In four of them, also with liver cirrhosis, HCC was found postoperatively (false negative). Three of these were incidental tumours (1 per cent) and the other one was a suspicious image with a negative preoperative citology. 11 of the 33 preoperative HCC with liver cirrhosis (33·3 per cent) showed no postoperative malignancy (false positive). pTNM classification for the patients with HCC (26) is shown in the table.

Year survival	Stage I (n=1)	Stage II (n=16*)	Stage III (n=5)	Stage IV A (n=4)	Global (n=26*)
1	0·0	0·81	0·4	0·75	0·69
2	0·0	0·75	0·4	0·75	0·65
3	0·0	0·69	0·4	0·75	0·61
4	0·0	0·69	0·4	0·75	0·61
5	0·0	0·69	0·4	0·75	0·61

*One with no liver cirrhosis

Okuda preoperation situation of HCC patients was as follows: 10 (40 per cent) stage I, 11 (44 per cent) stage II and 4 (16 per cent) stage III. When comparing the survival of the HCC and non-HCC groups by Kaplan-Meier method, the results were similar (0·615 for HCC and 0·696 for non HCC) with a follow up of 77 and 87 months, respectively). In summary, HCC incidence in our series was 0·18, with a 0·97 and 0·67 of specificity and sensitivity for HCC diagnoses respectively.

Conclusions: In our institution, as in many others, OLT has proved to be a useful alternative in the treatment of cirrhotic patients with HCC. Overall sensitivity for the HCC preoperative diagnoses is very poor in this group of patients. So, we think that, in the absence of more accurate diagnostic procedures, the staging efforts in cirrhotic patients with HCC who are candidates for OLT, are nowadays unhelpful.

Improved hemodynamics with temporary porto-caval shunt in orthotopic liver transplantation

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There are several theoretical and practical aspects to preserve the recipient vena cava during hepatectomy for orthotopic liver transplantation. However in patients with insufficient collateral circulation, excessive haemorrhage and major portal hypertension a veno-venous bypass or temporary porto-caval shunt alternatively can be used in order to maintain haemodynamic stability, adequate renal perfusion pressure and an undistended intestine to facilitate graft implantation. In the following study the experience with latero-lateral cavo-cavostomy for hepato-venous reconstruction is reviewed with and without the use of veno-venous bypass or temporary port-caval shunt.

Patients and methods: A total of 54 liver transplantations were analysed. In 38 transplantations a latero-lateral cavo-caval anastomosis was performed (Group I). In Group II (n=8) the same technique was performed, using a veno-venous bypass and in Group III (n=8) a temporary portal caval shunt was constructed. Patients were comparable with regards to age, Child Pugh, urgent/elective, preoperative mean creatinine, cardiac index, donor age, cold ischemia time and operating time.

Results: Mean arterial pressure (mmHg): Group I 128±34; Group II 114±28; Group III 108·6±32. Cardiac index decrease during the operation was 2·3±1·9, 1·5±0·6 and 1·2±1·0 respectively (P=0·05). The peroperative blood loss packed cells was 16·4±15·8 vs 4·5±10·5 vs 1·2±2·3 (P=0·004) and for fresh frozen plasma it was 19·0±14·7 vs 8·0±6·4 vs 3·7±4·0 (P=0·002). Course on ICU (days), liver function tests, renal function and the need for reoperation because of bleeding were not statistically significant different between the groups. One year patient survival was 82·7 per cent vs 69·4 per cent vs 85·7 per cent.

Conclusion: Despite preservation of the caval flow, the additional use of a temporary porto-caval shunt or a veno-venous bypass was advantageous with regards to operoperative haemorrhage as measured in loss of packed cells and fresh frozen plasma. There was no difference between the group of veno-venous bypass and porto-caval shunt. Cardiac index decreases less with the temporary porto-caval shunt and it appears to be suitable to avoid excessive portal hypertension and associated haemorrhage and potentially facilitates the implantation of the graft.

Ischaemic injury in donor hearts: immunohistochemical identification of complement membrane attack complex in the presence of normal histology

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Aim: Primary graft failure (PGF) is responsible for 15–20 per cent of early deaths following heart transplantation. Myocardial injury may occur as a consequence of catecholamine 'storm' at brainstem death, inadequate myocardial protection, or delayed reperfusion. Our aim was to investigate a novel technique for identification of myocardial ischaemic injury, with potential application to evaluation of donor hearts.

Methods: In order to assess myocardial injury prior to implantation, we investigated myocardial biopsies obtained at retrieval in 33 donor hearts by routine haemotoxylin-eosin histology, and immuno-histochemical identification of the C5b-9 complement membrane attack complex (MAC), a validated early marker of ischaemia*. Donor and recipient records were reviewed to establish inotrope requirement and outcome. Donor hearts were assessed by inspection and haemodynamic evaluation. Acceptance criteria included normal gross morphology, filling pressures <12 mmHg, and cardiac index >2·4 L/min/m^2 on minimal inotropic support.

Results: All donors had normal ECG patterns. All conventional histology was normal, but six biopsies (18 per cent) stained C9 positive. Of these, one heart was not implanted due to haemodynamic instability of the donor during retrieval, and two patients (40 per cent of implants) died of PGF. Two further patients (40 per cent of implants) in the C9 positive group required prolonged postoperative inotropic support. In the C9 negative group, 2/27 (7·4 per cent) died of PGF, compared to an overall unit 30 day survival of 90 per cent.

Conclusion: This pilot study identifies pre-retrieval myocardial ischaemic injury as an important contributor to recipient outcome, and suggests that improved techniques to evaluate donor hearts may reduce the incidence of primary graft dysfunction.

*J. Doran, A. Howie, J. Townend and R. Bonser. Detection of myocardial infarction by immuno-histochemical staining for C9 on formalin fixed, paraffin wax embedded section. *J Clin Pathol* 1996; 49: 34–7.

Use of sirolimus overcomes risk factor of African–American race

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Aim of study: Despite successful transplant operations, African–American renal transplant recipients experience a higher degree of graft loss due to an increased incidence of noncompliance, hypertension, mismatches for racially associated antigens, and resistance to immunosuppressants. 10-year results of renal transplantation, wherein 89 per cent were primary transplants and 11 per cent were re-transplants, document a greater efficacy of cyclosporine (CsA) over azathioprine (AZA) on patient (85 per cent vs. 80 per cent, P= 0·04) and graft survival. At 1, 2, 3, 4, 5, and 6 years, CsA provides significantly better graft survival than AZA-based regimens; however, by 10 years, the CsA results match with those of AZA. Although CsA (Sandimmune)-based therapy has limited impact on long-term survival rates, the addition of sirolimus (SRL) to the CsA regimen may offset the adverse impact of African–American race on patient and graft survival.

Materials and methods: 58 patients were treated with varying doses of SRL in addition to CsA therapy. At one year, we examined patient and graft survival. Log rank statistic tests were used to determine graft and patient survival rates.

Summary of results:

1-Year Graft and Patient Survival for 58 SRL-Treated Patients

	n	Graft survival	Patient survival
Black	15	86·7%	100%
White	43	92·7%	95·2%

P=NS

Conclusions: Addition of SRL to a CsA-based regimen overcomes the higher rates of graft loss and death among African–American renal transplant recipients. Thus, SRL represents a significant new addition to the immunosuppressive armamentarium. New drug strategies for improving rates of acute rejection among African–American patients will need to be assessed in the future.

Isolated lung transplantation for end-stage lung disease

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Since 1991 we have performed 37 isolated lung transplantations for end-stage pulmonary disease: 15 single (SLT) and 22 bilateral sequential (DLT) (1 bilateral lobar). Recipient diagnoses were: cystic fibrosis (13), chronic obstructive lung disease (11), pulmonary fibrosis (9), bronchiectasis (4). Two patients had undergone lung transplantation while on ventilatory support for respiratory failure (SLT for pulmonary fibrosis). Three patients required cardiopulmonary by-pass (2 SLT and 1 DLT) which was associated with increased transfusion requirement. In 13 cases the donor lungs were reduced with multiple GIA staplers to fit the size of the recipient. During SLT the bronchial anastomosis was protected with an intercostal muscle pedicle while during DLT we used only mediastinal fat tissue. Five patients died after SLT (33·3 per cent) (1 to 42 days). After SLT the remaining native lung was the site of early (pneumonia, overinflation, retention of secretions with atelectasis, haemothorax) and late complications (recurrent pneumothorax, progressive overinflation, aspergillosis, nocardiosis) in seven patients (47 per cent). Three patients (17·6 per cent) died after DLT (oesophageal perforation: 1; heart failure: 1; primary graft failure: 1). One-year survival for SLT and DLT is 66·7 per cent and 82 per cent respectively. One patient has obliterative bronchiolitis controlled with increased immunosuppression six years after SLT. Three patients have a bronchial stenosis treated with laser resection and stenting. Cytomegalovirus infection has been seen frequently (nine cases) but has responded well to treatment with Gancioclovir. Other complications were sternal infection (2), wound infection (2), renal failure (3), bleeding requiring reoperation (3) and psicosis (3). Isolated lung transplantation can be performed with acceptable morbidity and mortality in properly selected patients with a variety of end-stage lung diseases. Improvement in lung function and quality of life can be achieved with both SLT and DLT; however, after SLT the native lung may be the site of onset of serious complications; for this reason we tend to increase the indications to DLT even for non-septic lung diseases.

Assessment of cardiac rejection by magnetic resonance imaging (MRI) and spectroscopy (MRS)

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Objective: In experimental orthotopic cardiac transplantation magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and Echocardiography were compared as non invasive diagnostic tool for detection of cardiac rejection.

Methods: Six orthotopic cardiac transplantations were performed in the swine on cardiopulmonary bypass and immunosuppression (triple therapy) was tapered after 10 days to obtain increasing rejection. The following measurements were performed on a 1·5TGe Signa (double tuned flexi-coil, gradient echo cine and 2 D-CSI) and on an Acuson 128XP10 on postoperative day 1, 3, 10, 17, 24 and 31: MRI: cardiac function and LV-mass, MRS: 31 P MR-spectroscopy, Echocardiography (transthoracal) and Rejection grading (ISHLT/Texas).

Results:

1. MRI: LV function increased (EF=+17 per cent) and LV mass increased (+41 per cent) with time and increased rejection ($P<0{\cdot}05$).
2. MRS: A significant reduction of phosphocreatine to adenosine triphosphate (PCr/ATP) occurred when comparing pre- to postoperative exams (−17 per cent; $P<0{\cdot}01$).
3. Echocardiography: Wall thickness increased markedly postoperatively (+27 per cent intraventricular septum and +17 per cent left posterior wall) whereas per cent shortening (+6 per cent) and ejection fraction (+8·5 per cent) did not change significantly.
4. Pathology grading showed an increased rejection with time especially after tapering immunosuppression. At autopsy rejection was mild in 2, moderate in 1 and severe diffuse (ISHLT 3B/Texas 6–7) in 3 animals.

Conclusions: MR-imaging and spectroscopy seem to be a promising tool for non invasive assessment of rejection. A significant reduction of phosphocreatine to ATP occurred when cardiac rejection was present. Thus cardiac rejection may be detected non invasively by MR-imaging and spectroscopy in the animal.

Acute cholecystitis: different therapeutic attitudes in our service in the last 4 years (232 cases)

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Introduction: The commonly accepted approach in the treatment of acute cholecystitis is urgent cholecystectomy. Laporoscopy has renewed interest in the option of 'cooling' the inflammatory process, in order to subsequently carry out a programmed cholecystectomy through the technique mentioned. We present an analysis of the data collected on hospital stay and medico-surgical complications in both therapeutic options.

Material and methods: We studied 232 patients presenting as emergencies between January of 1994 and December of 1997 with diagnosis of acute cholecystitis. They were distributed in three groups: A) operated on in their first admission; B) patients with high risk for a general anesthesia, treated by percutaneous cholecystostomy; C) treated using 'cooling' of the process to be operated on in a second admission.

We analysed the simple and accumulated hospital stay, the index of medical and surgical complications and mortality with a 't-student' program.

Results: Acute cholecystitis: 232.

A group: 137, 35 with associated surgery.

B group: 16. New admission: 4, 2 new acute cholecystitis, 2 open cholecystectomy.

C group: 79. New admission: 41, 6 new acute cholecystitis, 12 open and 23 laparoscopic cholecystectomy.

	Patients	Mean age	Hospital stay	Accumulated stay by new cholecystitis	Accumulated stay by reentry for surgery	Medical complications	Infections	Deaths
A	137/232 (59·0%)	69·1	11	0	0	33/137 (24·0%)	14/137 (10·2%)	3/137 (2·1%)
B	16/232 (6·8%)	80·6	15·6	17·35	16·6 (open)	7/16 (43·7%)	4/16 (25%)	2/16 (12·5%)
C	79/232 (34·0%)	67·3	7·8	13·8	15·8 (open) 14·6 (lap)	17/79 (21·5%)	4/79 (5·0%)	2/79 (2·5%)

Conclusions: Urgent surgery seems the most suitable approach in acute cholecystitis to be a sure and effective procedure; the patient from a single admission, avoids the risk of recurrent pathology from cholelithiasis (new acute cholecystitis, biliary pancreatitis…), with shorter hospital stay, without an increase in morbidity or mortality, with the economic repercussion that this has furthermore for the health system.

Open cholecystectomy in the laparoscopic era: implications for surgical training

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Aim: The aim of this study was to review our experience of open cholecystectomy in the laparoscopic era.

Methods: Since July 1990 a total of 927 cholecystectomies have been performed in our unit. All patients who underwent open cholecystectomy were reviewed. These included 66 of 801 laparoscopic cholecystectomies converted to an open procedure (8·2 per cent) and 126 open cholecystectomies.

Results: Of the combined total of 192 patients treated by open cholecystectomy, there were 127 females and 65 males. 41 patients had elective open cholecystectomy during the transition year after the introduction of laparoscopic surgery. Thereafter the most common indications for open operation were, previous abdominal surgery (n=21), suspected malignancy (n=10) and empyema/mucocele (n=10). Indications for conversion in the 66 patients included anatomical uncertainty (n=42), empyema (n=11), bleeding (n=4) and technical problems (n=4). Two patients died post operatively (1 per cent). The overall complication rate was 23 per cent (n=44); cardiorespiratory (n=22), retained common bile duct stone (n=3), deep venous thrombosis (n=2), sub phrenic abscess (n=2), bile duct injury (n=2), wound infections (n=2), post op haemorrhage (n=2) and miscellaneous (n=9).

Conclusions: Even in the laparoscopic era open cholecystectomy is required in a percentage of patients, many of whom present with complicated biliary tract disease and associated morbidity. These patients require experienced surgical management which has major implications for surgical training.

Complications after surgical biliary-enteric drainage

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Aim: The aim of this study is to analyse the complications after biliary-enteric drainage in the management of obstructive jaundice.

Material and methods: Between 1989 and 1996, 253 surgical drainage procedures were performed in our Department: 44 sphincterotomy (SP), 183 choledochoduodenostomy (CD) and 26 hepaticojejunostomy (HJ).

In the case of SP there were four acute pancreatitis (nine per cent) one of them caused death. Residual choledocholitiasis was evidenced in three cases of the 35 SP practiced because of choledocholitiasis (8·5 per cent).

Biliar stricture appeared in two cases (4·5 per cent). 183 patients underwent CD. The complications were: three acute cholangitis (1·6 per cent), 2 anastomosis strictures (1 per cent) and 4 external biliary fistulae (2·7 per cent) three of them after drainage for malignant obstructive jaundice.

Postoperative complications in the case of hepaticojejunostomy were: 1 stricture of the anastomosis (3·8 per cent) and two biliary strictures (7·6 per cent).

Conclusions: Our results suggest that complications after drainage techniques are unusual but early diagnosis is necessary to reduce morbidity and mortality rates.

Double blind randomized controlled trial of buccal suscard versus placebo in the prevention of endoscopic retrograde pancreatographic induced pancreatitis

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Pancreatitis is the most common complication of Endoscopic Retrograde Cholangiopancreatography (ERCP) occurring in up to 30 per cent of patients. Previous studies have failed to show any benefit in the use of somatostatin or corticosteroids in decreasing its incidence. Sublingual glyceryl trinitrate relaxes the peri-ampullary sphincter muscle and may reduce pancreatic duct pressure thereby reducing the risk of ERCP induced pancreatitis.

186 patients were randomly allocated to receive either placebo (P) (n=96) or buccal suscard (BS) (n=90) 5 minutes pre-procedurally. At ERCP, sphincterotomy, stent insertion and stone extraction were undertaken as indicated. Six hours post-procedurally all patients were asked to quantify their pain and a serum amylase estimation was undertaken. Pancreatitis was defined as the presence of pain in conjunction with a serum amylase in excess of 1000 IU.

The overall cannulation rate was 92·5 per cent (172/186). There was no statistical difference in the cannulation rates between the two groups (P = 88/96 = 91·75 per cent) and (BS = 84/90 = 93·3 per cent).

Pancreatitis occurred in 17 patients in the P Group and seven patients in BS Group (P>0·05). The difference in proportions is 0·787 and the 95 per cent confidence intervals for the true difference is 0·699 to 0·875. Statistical analysis was by a Chi-squared test with Yates' correction.

Although buccal suscard has not been shown to significantly decrease ERCP induced pancreatitis the results do suggest that further work needs to be undertaken on this drug.

Serum CA19-9 and CEA: are they useful as early gallbladder cancer markers?

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Aim: To assess the feasibility of serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9) levels as early markers of chronic cholecystitis neoplastic degeneration related to gallstones. Benign conditions associated with a rise in serum CA19-9 levels would be identified.
Methods: A prospective study was undertaken of 75 consecutive operated patients of median age 71·8 (range 60–90) years due to symptomatic cholelithiasis. The study group was collected among subjects aged 60 years and over because of the late presentation of gallbladder cancer. There were 51 females and 24 males (ratio 2·1/1). One single surgeon and two pathologists performed the collection and histological study of the specimens, which were fixed in Carnoy and stained with hematoxylin and eosin. Serum CEA and CA19-9 levels were obtained on the day of operation.
Results: Of the 75 patients, 31 showed benign hepato-pancreato-bilary diseases associated with increasing CA19-9 serum levels: acute pancreatitis (12), obstructive jaundice (10), acute cholecystitis (6) and cirrhosis (3). However, only two patients showed a slight increase over normal serum CEA levels. The first one suffered an acute cholecystitis with an unsuspected gallbladder adenocarcinoma and miliary liver metastases (CEA: 7·2 ng.ml, CA19-9:83·5 u/ml); the other one had cirrhosis (CEA: 7·5 ng/ml, CA19-9:45·6 u/ml). Of the remaining 44 patients, the median serum markers levels among the different epithelial findings were: normal (n=21, CEA=2·5 ng/ml, CA19-9=15·8 u/ml) hyperplasia (n=12, CEA=2·1 ng/ml, CA19-9=12·5 u/ml), gastric metaplasia (n=10, CEA=4·9 ng/ml, CA19-9=9·9 u/ml), dysplasia (n=4, CEA=3·9 ng/ml, CA19-9=15·7 u/ml), intestinal metaplasia (n=3, CEA=5·5 ng/ml, CA19-9=11·3 u/ml), and adenocarcinoma (n=1, CEA=7·7 ng/ml, CA19-9=5·1 u/ml).
Conclusions: 1) Some benign conditions should be strongly taken into account when serum CA19-9 is measured. 2) There are no significant increases of serum CA19-9 values related to different gallbladder epithelial features. 3) Normal serum CA19-9 and CEA cutoffs are not useful as markers of early neoplastic epithelial gallbladder changes.

Endoscopic retrograde cholangio-pancreatography (ERCP) and its complications

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Introduction: ERCP is an important method in the diagnosis and the treatment of pancreaticobiliary diseases. The incidence of biliary sepsis is 2–15 per cent in ERCP interventions and it is the most important among the major total complications of ERCP. Thus, in order to evaluate the causes and the complications related to ERCP, having been performed in our 4th surgery clinic, we planned this study.
Patients and methods: 110 patients of 4th surgery clinic who underwent ERCP between the years of 1991 and 1997 were evaluated retrospectively. Patients were evaluated on the bases of; age, gender, ERCP indications, clinical diagnosis, previous biliary surgery, diagnostic method and interventions, performed surgical methods, complications and postoperative morbidity and mortality. The statistical analyses were evaluated with Chi-Square (Pearson) test $P<0{\cdot}05$ were accepted as statistically significant.
Results: In this series of 110 patients, 97 patients (88·2 per cent) underwent ERCP preoperatively and 13 patients (11·9 per cent), postoperatively. In all cases, broad spectrum antibiotics were administered before and after this intervention. 54 (49·1 per cent) patients were male and 56 (50·9 per cent) patients were female. 34 cases were over 65 years old (30·9 per cent) and 76 cases were under 65 years of age (69·1 per cent). Mean age were 55·4 (17–86). The results of ERCP: six patients were assessed as normal (5·5 per cent), 72 patients were assessed as benign (65·4 per cent) but malignant pathology was identified in 32 cases (29·1 per cent) ($P<0{\cdot}001$). ERCP could not be performed in 10 patients due to different reasons (9·1 per cent). After ERCP 9 patients developed biliary sepsis (8·2 per cent), three patients developed bleeding (8·2 per cent), one patient developed common bile duct perforation (0·9 per cent). Another patient died during ERCP due to internal medical pathology. It was observed that 20 cases had been operated for biliary tract problems previously (18·2 per cent) and the complication ratio in this group were 30 per cent ($P<0{\cdot}01$). There were biliary tract dilatations in 80 patients (72·7 per cent) and the complications were found in 11 patients (13·8 per cent) ($P<0{\cdot}05$). Biliary sepsis was not found in patients in whom the ECRP could not pass proximal to the site of the lesion. Nasobiliary stent and transient 7F plastic stent were applied to 4 (3·6 per cent) and 2 (1·8 per cent) patients respectively and the complication rates were 28·6 per cent and 14·3 per cent respectively ($P<0{\cdot}05$). 83 cases were operated (75·5 per cent) perioperative mortality was 6·4 per cent (n=7) and the overall mortality were 15·5 per cent (n=17).
Conclusion: The most important reason for mortality and morbidity after ERCP is biliary sepsis and its rate was found as 8·2 per cent in this study. The complication rates were found to be high in patients with malignancy, previously operated biliary tract, dilatation of biliary tract, nasobiliary stents. We think that the reason why the complication rates were high in nasobiliary stent patients would be the inability to maintain asepsis and to perform adequate drainage from NBS.

The incidental finding of gallbladder carcinoma in elective laporoscopic cholecystectomy – does it fulfil the requirements of oncological surgery?

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Aim: Still we find hints in literature, that the incidentally diagnosed carcinoma of the gall bladder in laporoscopic cholecystectomy is affiliated with a good prognosis. We wanted to investigate retrospectively, whether in our patients this statement is justified.
Material and methods: From October 1987 to August 1997, 28 patients with carcinoma of the gall bladder underwent operation in our hospital. In 13 patients the diagnosis was known preoperatively, in 15 the diagnosis was confirmed intraoperatively (n=5) or postoperatively (n=10). For our retrospective analysis we used the data from our oncological follow-up, in which most of our patients took part.
Results: The prognosis of patients operated under the diagnosis of gall bladder cancer was expectedly poor: only four were operated in a curative manner, their mean survival was 5·5 months. The palliatively operated had a mean survival of only 1 month. All these patients died within 23 months.

The prognosis of incidentally diagnosed gall bladder cancer was poor as well.

In all of our 15 patients the first operation was an open or laparascopic cholecystectomy. A second, extended operation could not be performed in 11 patients due to manifest liver metastasis, lymphangiosis carcinomatosa or lymph node metastasis or poor general condition in elderly patients. Within this group, two are still living, one with manifest liver metastasis (16th postoperative month), the other without tumour evidence (8th postoperative month).

An extended secondary operation was planned in four cases. Since one had liver metastasis found in the second operation, it could be performed in only three. Of these three, one lives for six months, another for 11 months postoperatively without any evidence of tumour recurrence. The third died in the 9th postoperative month of liver metastasis.

Of four patients with T1 stages without second operation, two elderly patients were lost from our follow up, one died in the 13th postoperative month, the other lives in the 16th postoperative month with manifest liver metastasis.
Conclusion: As well as the primary diagnosis of gall bladder carcinoma, the incidental finding of an carcinoma in elective cholecystectomy is affiliated with an extremely poor prognosis. The only option to improve survival time slightly seems to be extended surgery to clear the liver bed of the gall bladder with wide margins. In any case of proved gall bladder carcinoma, the operation should be performed as open surgery. With questionable intraoperative findings, early conversion to open surgery is recommended.

Complex therapy of gallbladder carcinoma

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Malignant tumours of the gallbladder represent an unsolved problem of surgery, with poor immediate and late results. Aim of the study was to evaluate the results of complex oncological therapy of gallbladder carcinoma.

From 1989 to 1997 108 patients for primary malignancy of the gallbladder were admitted to our institutions. 80 per cent of them were female, mean age of the whole group was 66·5 years respectively. Concomitant gallstones were detected in 54 patients (50 per cent). Radical surgery with partial liver resection and/or hilar lymph node block dissection was possible in 36 patients. Biliary or gastrojejunal bypass has been applied for palliation in 24 cases. Advanced tumour mass was found in 48 patients, where only laparotomy, or FNAB was performed. In these group of patients ERC, PTD succeeded in only 20·4 per cent. Chemoembolization as adjuvant treatment after resection was applied in eight cases, for palliation, in four. Percutaneous ethanol injection was used in four cases. Intraarterial chemotherapy via hepatic arterial port was administered in six. Metastases of the primary tumour were seen in the liver (42 patients), regional lymph nodes (10 patients) lungs (5 patients), peritoneum (seven patients), kidney (one patient). Radical resection, with hilar lymph node dissection gives hope for the patients. 62 per cent of radically operated patients are living after two years. Liver infiltration and/or distant metastases represent a poor prognosis however. Palliative endoscopic or transhepatic drainage procedures have minimal chance for success.

Therapeutic options for iatrogenic biliary lesions following open and laporoscopic surgery

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Iatrogenic biliary lesions were and still are a very serious event caused by accidental surgical trauma (ligature or section) due to inadequate identification of biliary and vascular elements, or to extensive dissection which damages the vascular microcirculation of the common bile duct, causing ischaemic necrosis with consequent formation of biliary fistulae or stenosis. On the other hand biliary stenosis may occur by using for haemostasis inadequate nonresorbable suture lines, causing granulomatous lesions or sclerosis of the common bile duct. The prognosis for this pathology is closely correlated with the timing of discovery of the lesions.

The authors present their experience on 53 surgical procedures done to correct some incidental injuries of the common bile duct, during 30 years of practice. In this presentation are discussed the essential factors that affect the difficulty of correctional procedures and the technical options reserved for each case.

Particularly aspects of reconstruction, or replacement of the common bile duct are presented, adding some original procedures (hepaticojejunostomy without suture or colangioomphalo-choledocostomy).

Of the many external drainage techniques of the common bile duct, the authors prefer the axial biliary trans-choledocohepatic drainage. It represents one of the only possible procedures after choledochojejunostomy and after hepatico-enteric anastomosis in Glisson's capsule. It is also the elective procedure for drainage and calibration in reparative biliary surgery, or after reimplantation of the common bile duct.

Early failure of intestinal barrier function and endotoxaemia in severe acute pancreatitis

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Aim of the study: This study investigated intestinal permeability in healthy controls and patients with acute pancreatitis, its relationship with severity, and evidence for endotoxaemia.
Materials and methods: Polyethylene glycol (PEG) 400 and PEG 3350 were selected to determine micromolecular and macromolecular intestinal permeability. PEG 400 (5 g) and PEG 3350 (40 g) were administered enterally. Urinary PEG molecules were measured by high-performance liquid chromatography. Samples were completed within 72 hours of symptoms onset. Attacks were classified as mild or severe by the Atlanta Criteria. APACHE-II scores, C-reactive protein (CRP) levels and endotoxin and anti-endotoxin antibodies were determined on admission. There were 75 subjects: 23 healthy controls; 36 mild and 16 severe attacks.
Summary of results: Median admission APACHE-II was 10 in severe and five in mild attacks, median peak CRP 279 mg/l in severe and 90 mg/l in mild attacks. Urinary recovery of PEG 400 was similar in all groups, but that of PEG 3350 was significantly greater in severe attacks (median 0·46 per cent, range 0·04–10·8 per cent) compared with mild attacks (median 0·08 per cent, range 0·05–0·26 per cent) and controls (median 0·12 per cent, range 0·05–0·22 per cent) (both $P<0·001$). Endotoxaemia was detected more frequently in severe compared with mild attacks (50 per cent vs. 22 per cent), and at greater levels (median 0·035 EU/ml vs. 0·01 EU/ml). Anti-endotoxin IgG levels were significantly lower in severe compared with mild attacks (median 65·8 vs. 111 GMU, $P<0·01$).
Conclusion: The results suggest that intestinal barrier function is impaired early in the course of severe acute pancreatitis. This may play an important role in the pathogenesis of Multiple Organ Failure and superinfection of pancreatic necrosis.

Prognostic factors for survival of patients with tumours of the pancreatic head

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Retrospective study was performed to measure the possible prognostic factors for survival after radical surgery in patients with carcinoma of the pancreatic head.

29 patients underwent pancreaticoduodenectomy for cancers of the pancreatic head (n=22) and the papilla of Vater (n=7). In seven patients Whipple's procedure was performed, and pylorus preserving pancreaticoduodenectomy was carried out in 22 cases. Using flow cytometry the authors measured the nuclear DNA content of tumour cells.

Median survival of patients with the carcinoma of pancreatic head was 9·3 months. Survival in patients with cancer of papilla of Vater was 20·5 months. The difference was significant. Tumour size and poor differentiation grade had negative influence on survival in patients with tumour of the pancreatic head region. There was no significant correlation between the lymph node involvement and the survival.

Of the 22 pancreatic carcinomas 14 were diploid and eight were aneuploid. The survival was 10 months in case of diploid carcinoma, and it was eight months in case of aneuploid cancer. Six diploid and one aneuploid tumours occurred in the group of cancer of papilla of Vater. In this group the survival of the patients with diploid tumour was 17 months, and it was 40 months with the aneuploid tumour.

The mean proliferation index (PI) of the diploid pancreatic cancers was 9·7 per cent, whereas that of the aneuploid pancreatic cancers was 13·3 per cent. The mean PI of the diploid tumour of papilla of Vater was 7·5 per cent and the PI of aneuploid tumour was 28 per cent. The PI was significantly higher in aneuploid cases. There was no significant correlation between the PI and the survival.

The survival of high-grade (Grade I-II) pancreatic carcinomas was 10·9 months, and the survival of low-grade (Grade III-IV) tumours was 7·8 months. The low-grade carcinomas occured in a significantly higher rate in aneuploid cases (6/8), than in diploid cases (5/14). The PI was significantly higher in low-grade tumours.

In conclusion, the tumour size and poor differentiation grade were negative prognostic factors for the survival. DNA ploidy and PI had no significant effect on the survival.

Acute pancreatitis: surgical approach in an emergency department

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Over a 26 month period, from October 1995 to November 1997, 65 patients with acute abdominal pain and suspected acute pancreatitis were admitted to the Emergency Surgery Unit of S. Orsola, Malpighi Hospital in Bologna, Chief Prof. O. Campione.

Clinical diagnosis was supported by typical clinical manifestations and by values of serum amylase and/or serum lipase in excess of three times the upper limit of normal.

Abdominal ultrasound and CT scan were performed within 24–48 hours of hospitalization, in order to confirm the clinical diagnosis and to distinguish interstitial from necrotizing pancreatitis.

33 of 65 patients were males with age ranging from 16 to 87 (average 56), and 32 were females with age ranging from 22 to 95 (average 66).

Among our cases, 47 patients (72 per cent) had biliary pancreatitis and 12 (18 per cent) had alcoholic pancreatitis; in four cases (six per cent) the etiology was post-operative, and three cases (four per cent) had post-endoscopic retrograde cholangiography (ERCP) pancreatitis.

In 17 patients (12 with biliary, three alcoholic and two post-operative pancreatitis) surgery was performed for infected pancreatic necrosis or for sterile necrosis without clinical improvement after one or two weeks of intensive care therapy, or if evidence of organ failure and systemic complications had intensified.

Surgical debridement of necrosis was performed.

Five patients (two with alcoholic, one gallstones and two post-operative pancreatitis) died.

18 out of 47 patients with pancreatitis caused by gallstones (38 per cent) underwent urgent endoscopic retrograde cholangiography which was performed within 72 hours from the onset of symptoms, because of obstructive jaundice and/or biliary sepsis.

In 16 patients (88 per cent) ERCP showed gallstones or sludge in the common bile duct, and a sphincterotomy was performed and gallstones were removed.

Urgent ERCP reduced the severity of pancreatitis and relieved biliary sepsis.

Eight out of 16 patients (50 per cent) didn't undergo cholecystectomy because of high operative risk.

In our experience, a multidisicplinary approach including medical therapy or intensive care therapy according to the severity of pancreatitis, radiologic evaluation, careful monitoring and surgical therapy, represent the optimal management of patients with acute pancreatitis, selecting the strategy best suited to the individual clinical situation.

Effects of gabexate-mesilate on pancreatic juice: experimental and clinical results

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Aim of the study: To assess the pancreatic inhibitory action of Gabexate-Mesilate (GM) in pancreatic juice and serum in an experimental model and in human subjects.

Material and methods: Five female pigs each weighing 130 kg were used for the experiments. After laparotomy, the pancreas was transected and the pancreatic duct cannulated. GM (1000 mg/24 h) was intravenously infused and samples of blood and pancreatic juice were taken at 0, 24, 48 and 72 ore for determination of Phospholipase A2 and amylase activity and GM inactive metabolite (ethyl-p-hydroxy-benzoate).

We also assessed GM activity in four patients: two had pancreatic duct drainage placed after duodenopancreatectomy; and two had pancreatic drainage after pancreatic resection. GM was injected at 900 mg/24 h and samples of blood and pancreatic juice were taken before, during and after G.M. infusion for six days. During the second week, as an adjunct to GM, patients received subcutaneous injection of octreotide (0·3 mg/24 h). Samples of pancreatic juice and serum were assayed for phospholipase A2, amylase and the GM metabolite, and the pancreatic secretion was measured.

Results: In pigs and in human subjects GM infusion led to detectable GM metabolites in pancreatic juice and serum. GM reduced enzymatic activity in serum and pancreatic juice in a dose-dependent manner but left the volume of pancreatic juice unchanged. Conversely octreotide injection left enzymatic activity unchanged but significantly decreased pancreatic secretion in humans.

Conclusions: G.M. acts as an enzyme inhibitor within the pancreatic ducts. This finding confirms the rationale underlying its use in reducing the incidence of severe complications in patients with acute pancreatitis. Combined treatment with octreotide and GM is useful because these two drugs inhibit pancreatic secretion in two different ways.

Nitric oxide and heparin but not procaine improves blood perfusion of the pancreas in acute experimental pancreatitis

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The aim of the study was to investigate the influence of a nitric oxide donor (L-arginine), heparin and procaine on the microcirculation of the pancreas in acute cerulein-induced pancreatitis (AP) in rats. AP was induced in 48 rats (12 animals in each group) by four intraperitoneal cerulein injections 15 µg/kg/h. Microcirculatory values of the pancreas were measured by means of laser Doppler flowmetry. The pancreatic capillaries' morphometry (the amount of open/closed vessels, the capillary diameter, sum of open capillaries' areas/mm^2 of the tissue) was carried out upon the capillaries stained with monoclonal antibody against von Willebrand's endothelial antigen. The animals were divided into the groups: Group I – AP receiving no treatment; Group II – AP treated with L-arginine 2×100 mg/kg; Group III – AP treated with heparin 2×2·5 mg/kg; Group IV – AP treated with procaine 2×25 mg/kg. Acute pancreatitis resulted in a fall of pancreatic perfusion to 37 per cent as compared to the basal values of healthy animals, measured by laser Doppler flowmetry. L-arginine and heparin injections improved the pancreatic perfusion to 72 per cent and 76 per cent respectively. In the group I the percentage of open capillaries was calculated as 37 per cent. L-arginine and heparin treatment increased the amount of open capillaries up to 52 per cent and 54 per cent. The L-arginine and heparin administration increased twice the sum of open capillaries' areas as compared to the AP group without treatment. Procaine therapy had no effect on impaired pancreatic microcirculation in AP. Authors conclude that nitric oxide and heparin improve the pancreatic blood perfusion in AP and may be considered as therapeutic agents preventing the pancreatic necrosis.

Endocrine function of the pancreas following storage with HTK or UW solution and transplantation

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HTK (Histidine Tryptophan Ketoglutarate) solution is used with increasing frequency for cardiac, renal and hepatic transplantation. For pancreatic grafts this solution has not been used routinely, essentially due to the lack of experimental data. In the following study HTK solution was used compared to UW solution for 24 hours cold storage of porcine segmental pancreatic grafts prior to autotransplantation.

Material and methods: Landrace pigs underwent total pancreatectomy including the coeliac trunk, the splenic artery and the proximal common hepatic artery as arterial vascular pedicle and the splenic vein as the venous vascular pedicle. The arterial pedicle was flushed ex situ, either with HTK (GI) or UW (GII) (50 to 100 cc until the venous effluent was clear for at least 5 minutes, perfusion pressure 60 cm H_2O). Thereafter the grafts were stored for 24 hours at 4°C. For the induction of diabetes the right lobe of the pancreas was totally resected with preservation of the duodenal arcade. After 24 hours the pancreas was transplanted to the iliac fossa. Exocrine drainage was performed into the peritoneal cavity. Daily fasting bloodglucose levels were normal <100 mg/dl and glucosuria was absent. Untreated unoperated pigs served as normal controls and totally pancreatectomized animals served as diabetic controls. IVGTT was performed within seven days post-transplant by intravenous injection of 0·5 g/kg glucose and sampling serum glucose at 0–1–3–5–10–20–30–60–90 and 180 minutes. K-values were calculated.

Results: In GI (HTK) 8/8 were normoglycemic after transplantation. The mean K-value was −1·33±0·81. Glucosuria was absent in all animals. In G II (UW) 6/6 animals were normoglycemic; the mean K-value was −1·50±0·83 (P vs GI 0·45). Mean K-value of totally pancreatectomized animals was −0·52±0·19 (P<0·008 vs functioning grafts). Glucosuria in pancreatectomized animals was maximal. The mean change in wet weight of the pancreas grafts was 3·01±2·2 g in GI and −1·0±3·6 g in GII (P=0·17).

Conclusion: 24 hours cold storage (4°C) of the porcine pancreas, using HTK solution provides reliable graft function following autotransplantation as obtained for storage with UW solution.

Repeated laporotomy for infected pancreatic necrosis

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Aim: Evaluation of the method of repeated laporotomy in patients with infected pancreatic necrosis.

Material: In the years 1984–1997, 48 patients with infected pancreatic necrosis were treated by the repeated laporotomy. The most common reason of infected necrosis was acute pancreatitis (25 patients) and as a complication of ERCP (six patients). In all cases an elevated body temperature was noted, and in 16 patients initial signs of multiorgan failure were noted. Necrosis was visualized by ultrasound in 62 per cent of cases (23 patients), and by CT scans in 100 per cent.

Results: All patients were treated according to Bradley's procedure. 11 hospital deaths (37 per cent) were noted. Most common reason was multiorgan failure (14 patients). In 12 patients (23 per cent) complications were noted. These were: jejunal and colic fistulae and bleeding from retroperitoneal vessels. The follow-up period of 28 living patients was three months to 13 years. During this time proper endo- and exocrine function of the remaining pancreatic tissue and lack of any fluid collections were documented.

Conclusions: Repeated laporotomy is an effective method of treatment of patients with infected pancreatic necrosis. It enables proper view of the retroperitoneal space and good control in complicated cases.

Fulminant pancreatitis

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In 1992 a clinically-based classification system for acute pancreatitis (AP), was proposed at Atlanta Symposium. Fulminant pancreatitis (FP) is a non-agreed definition, but some patients with severe AP develop an early fulminant and lethal progress of the disease. For defining FP, we propose those severe AP cases which, within the first 48 hours of the onset of the symptoms, show failure in three or more organs (multisystemic organ failure: MOF).

Methods: Patients having AP of any etiology were prospectively studied in three surgical centers over the last seven years. Our aim was to analyse fulminant cases in severe AP, and we detected incidence, etiology, organ involvement in MOF and mortality. Severity was determined by APACHE II (severe cases: >15 points) and our Original INDEX (severe cases: >0·40). Mortality referred to those hospitalized cases.

Results: 48 severe cases were detected, and 13 (27 per cent) were fulminant. Etiology was gall stone in six, alcoholic in four, dislipemic in one, post ERCP in one, and post surgical papillotomy in one. All of FP were MOF with these organ functions involved: lung and kidney in all 13, heart in 9, liver in 8, endocrine pancreas in 8, brain in 8, hemostatic in 3. The mean APACHE II average was 27±6 and the INDEX was 0·54±0·6. All patients were treated in ICU with a multidisciplinary approach, and 11 of 13 (85 per cent) died after many complications during the treatment. Mortality in non-fulminant severe cases was 4 of 35 (11 per cent) (X2: $P<0{\cdot}01$).

Conclusion: Fulminant pancreatitis is a special entity in severe cases of AP with a MOF detected before 48 hours after the onset of the symptoms, with a mortality of 85 per cent of the patients. Necessity of an agreed definition is mandatory to perform new treatment modalities and strategies to subdue this lethal entity.

Acute pancreatitis – diagnostic and surgical procedures in Poland – 15 years review

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We analysed inquiries from 71 surgical units in Poland in the period 1981–1991. The inquiry consisted of the following parts: number of cases of AP in the last 10 years, sex, age, etiological factor, form of AP, diagnostic tools, treatment modalities, mortality rate. In the period 1981 to 1991, 8866 patients with AP were admitted to surgical departments (4300 male and 4566 female). The average age was 52·2 years, patients' age ranged between 16–81 years. The data concerning 230 cases of AP treated from 1968 to 1996 were precisely analysed (139 female and 91 male, average age 51). The patients were stratified according to the Trapnell's and APACHE II scores. Patients were divided into two groups: Group A – included 16 patients treated between 1968–1985. Group B – included 30 patients treated from 1986 up to 1995. The data of 8866 patients with acute pancreatitis – biliary in 53 per cent, alcohol and other in 47 per cent. 74 per cent had oedematous pancreatitis, 26 per cent necrotizing form of the disease. In four per cent of all the patients computed tomography was performed. 66 per cent of patients were treated conservatively with the mortality rate of 3·5 per cent. 34 per cent of the patients underwent surgery with the mortality rate 23 per cent. Data collected by the authors (230 patients with AP) revealed biliary pancreatitis in 56 per cent of the cases and in 44 per cent the alcohol etiology. Oedematous form of AP was diagnosed in 73 per cent, necrotizing pancreatitis – in 17 per cent of the cases. In 46 patients with necrotizing pancreatitis, bacterial infection was confirmed. These 46 patients are the subject for the further analysis in this work. Mortality rate in the patients of group A was 81 per cent. The mortality rate in group B significantly decreased to 48 per cent. Hospital stay period of the patients that survived infected AP was between 27 to 122 days.

POSTER PRESENTATIONS

Spleen

The effect of splenectomy and splenic autotransplantation onto blood lipid levels

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Experimental and clinic studies have been shown that spleen may have some effect on the lipid metabolism. It has been shown that serum cholesterol levels have been found to be low in patients with hypersplenism and this has been reversed to normal levels following splenectomy. Also the incidence of atherosclerotic cardiovascular disease has increased in patients who have had a splenectomy following trauma.

In the current study, the effect of splenectomy and splenic autotransplantation on the blood lipid levels were investigated. Forty rats were studied and preoperative total triglyceride, total cholesterol, HDL, LDL and VLDL levels were determined.

Rats were classified to five groups based on the surgical procedures.

Group S	(*n*=8 rat)	Sham group
Group SP-N	(*n*=8 rat)	Splenectomy + normal diet
Group SP-C	(*n*=8 rat)	Splenectomy + % 1 cholesterol diet
Group SA-N	(*n*=8 rat)	Splenicautotransplantation + normal diet
Group SA-C	(*n*=8 rat)	Splenicautotransplantation + % 1 cholesterol diet

An active splenic function was shown in rats who underwent splenic autotransplantation in both groups by using technician 99m sulphocolloid scintigraphy on day 30. Blood lipid levels were repeated 6 months later.

There was no difference between pre and postoperative lipid levels in sham group and SA-N group ($P>0·05$). All lipid levels including HDL are increased significantly in SP-C group ($P<0·05$). Also, VLDL and total triglyceride levels are increased significantly in SP-N and SA-C group ($P<0·05$).

This study showed that the spleen may have an important effect on the lipid metabolism and splenic autotransplantation may be protective in conditions in which the lipid levels are increased.

Eleven years of experience in nonoperative management of splenic injuries

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Aim: To evaluate the effectiveness of a conservative policy initiated in 1986 with regard to splenic injuries.

Materials and methods: From 1986 to the present, all patients with abdominal injuries, admitted to our hospital, who were haemodynamically stable, were given computed tomography (CT) to detect visceral intra-abdominal injuries. If the existence of splenic injury was confirmed, the therapeutic protocol was based on complete bed rest, and monitoring of the hemodynamic condition. Surgical exploration was only performed in the presence of one of the following conditions: penetrating abdominal injury, associated abdominal injuries which required surgery, blood dyscrasia, abnormal spleen, or persistence of haemorrhage (after the administration of up to four units of packed red blood cells) or recurrence of the haemorrhage.

Results: Two hundred and three patients, 166 male and 37 female, were admitted with splenic injuries during the study period. Ages ranged from 8 to 87 years old (mean 29·9). The principal mechanism of injury were vehicle accidents (132 cases). In eight patients immediate surgical intervention was necessary, in the other 195 patients, a conservative protocol was followed and in only 42 cases was surgical intervention necessary because of the afore-mentioned indications. Intervention was carried out at the moment of hospitalization or during the observation period. In 153 cases, spontaneous resolution of the splenic injury was achieved and confirmed by CT with an average hospital stay of 28 days; 56 of these patients needed a transfusion (mean 2·8 units of blood) and five patients died as a result of irreversible neurological injuries.

Conclusion: In our experience, early laparotomy in splenic injuries may be substituted for a nonoperative therapy protocol, whatever the age of the patient, with surgical intervention indicated for limited cases only.

Appendix

Diagnostic laparoscopy to exclude appendicitis is only useful in women of child bearing age

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Aim: A prospective audit of diagnostic laparscopy for patients with suspected appendicitis was revisited after a two year period to 'close the loop'. Open appendicectomy is encouraged as a training operation at this hospital.

Material and Methods: Two hundred and eighty two patients were taken to theatre with a suspected diagnosis of acute appendicitis. Of these 145 (51 per cent) had laparoscopy; 116 had subsequent appendicectomy. The remaining 137 patients (49 per cent) had appendicectomy without preliminary laparascopy (the majority being men or children with clear signs and symptoms).

Results: Twenty nine patients were spared unnecessary appendicectomy following laparoscopy; all but one being women of child bearing age. However, 116 patients had appendicectomy, of whom 31 (21 per cent) had a clinically and histologically normal appendix; 85 (59 per cent) were inflamed with 23 (16 per cent) perforations. Of those who did not have laparoscopy 29 (21 per cent) had a normal appendix removed, 108 (79 per cent) were inflamed with 35 (32 per cent) perforations. Operating times were prolonged in the laparoscopy group (62 min; range 2–240) compared to open operation alone (53 min; range 15–250). There were no differences in length of postoperative stay (4·2 days, range 1–16 vs 4·6 days, range 1–17).

Conclusion: Women of child bearing age benefit from preliminary diagnostic laparoscopy to avoid unnecessary open operation. For all other patients open appendicectomy is appropriate based on clinical signs and symptoms and should be retained as a training operation.

Duration of symptoms is not related to pathology in acute appendicitis

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Aim: To detect relationship between duration of symptoms and histologically proven appendiceal inflammation level.

Material and methods: One hundred and forty six patients who underwent appendicectomy at one institution between January 1991 and October 1995 have been surveyed. Patients with other aetiologies of an acute abdomen (adnexitis, rupture of ovarian cysts, torsion of greater omentum) were excluded. The group consisted of 108 male and 38 female with age range between 14 and 68 years.

Results:

	Duration of symptoms (hours)					
Groups	Mean	Median	Minimum	Maximum	Standard deviation	Skewness
Catarrhal appendicitis	43·7	24	5	144	5·2	1·23
Phlegmonous appendicitis	36·1	24	6	120	30·8	1·45
Gangrenous appendicitis	41·6	24	12	140	32·9	1·75

Duration of symptoms did not differ significantly between groups (Kruskal-Wallis ANOVA median test).

Conclusion: The stage of inflammatory process during acute appendicitis does not depend on duration of symptoms.

Schistosomal appendicitis

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Aim: The appendix is commonly infested in schistosomiasis. It is not known if this is a predisposing factor for appendicitis or a mere coincidental histological finding.

Material and methods: A total of 56 patients (51 males; 5 females) underwent appendictomy for 'schistosomal' appendicitis over 10 year period. The histological slides of 41 (73·2 per cent) patients were retrospectively studied.

Results: The highest incidence was in the age groups 21–40 years. All excised appendices showed ova within their walls especially in the submucosal layer. The most common tissue response were submucosal fibrosis (92·7 per cent) and eosinophilia (87·8 per cent), followed by presence of suppurative inflammation (80·5 per cent). Granulomatous reaction was evident in 13 cases only (31·7 per cent). A striking feature was atrophy of submucosal lymphoid follicles in 70·7 per cent of cases. Hyperplasia of lymphoid follicles and serosal granulomas were rare (2·4 per cent). Similar tissue responses were histologically seen in four normal appendices examined.

Conclusion: Appendiceal infestation may predispose to appendicitis in the majority of affected cases but in some cases, it may well be a mere coincidental histological finding. Preoperative knowledge bears no clinical significance and does not alter management. However, the search for and treatment of active disease may be lacking in areas where follow up is a problem.

Acute appendicitis: impact of ultrasonographic visualization of the normal and abnormal appendix

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Aim: To improve the accuracy of clinical diagnosis in patients with suspected appendicitis, an attempt was made with high resolution broad band width (5–10 MHz) ultrasound transducers to visualise both the normal and abnormal appendix.

Material and methods: One hundred consecutive patients were evaluated. The visibility of the appendix, its AP outer diameter during compression (OD), the maximal wall thickness (MWT) and the presence of colour Doppler (CD) signs were recorded in all cases. The sonographic results were compared to operative and pathological results in all operated cases (38) and in 62 cases a 2 weeks clinical follow up was made.

Results: The appendix was visualised in all pathologically positive cases and in 82·5 per cent of the normal appendices (18·7 per cent partly, 63·8 per cent in whole length). The OD was greater than 6 mm in all true positive appendicitis cases, but also in seven of the normal appendices. Thus, using larger than 6 mm OD as the sonographic criteria of appendicitis resulted in unnecessarily operated false positive cases (100 per cent sensitivity, 91·3 per cent specificity, 74 per cent positive predictive value and 100 per cent negative predictive value). The false positive rate decreased, but the sensitivity also, if using MWT>3 mm as the diagnostic criteria (90 per cent sensitivity, 97·5 per cent specificity, 90 per cent positive predictive and 97·5 per cent negative predictive value). Adding CD improved specificity, but decreased sensitivity in both methods.

Conclusion: The normal appendix can be detected more frequently by ultrasonography than reported previously. Whole length demonstration of an appendix, smaller has 6 mm in OD is 100 per cent specific for a normal appendix. This sign might prevent unnecessary laparotomies in clinically doubtful cases. However, sonographic visualization of the appendix does not solve all diagnostic problems. While smaller than 6 mm OD means normal appendix, larger diameters do not necessarily indicate appendicitis. The specificity can be increased if MWT and CD signs are also evaluated.

Increased serum lipofuscin after renal transplantation

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Lipofuscin is believed to be the last product of lipid peroxidation. Elevated serum lipofuscin is a prognostic factor of multiple organ failure after major surgery.
Aim: To compare serum lipofuscin level after renal transplantation, hemodialysed patients and well matched healthy adults.
Material and methods: Lipofuscin has been determined according to Tsuchida with Roumen's modification and expressed in arbitrary units (u.), in serum of 56 healthy adults, 16 renal transplant recipients and nine hemodialysed patients. Age and sex were not significantly different between groups. Serum creatinine and urea levels did not differ significantly between hemodialysed and transplanted patients. Blood was collected before hemodialysis in uremic patients, or within 12 h and 7, 14, 21 days after renal transplantation.
Results: Serum lipofuscin in healthy adults was 231±69 u. In hemodialysed patients and renal recipients was increased significantly to about 150 per cent (364·6±150 u.) and 250 per cent (577±188 u.) respectively. Patients with transplanted kidney have revealed elevated serum lipofuscin level during 21 days after transplantation.
Conclusion: Elevated serum lipofuscin levels after renal transplantations show high oxidative stress due to several mechanisms of lipid peroxidation in this group of patients.

Selective continuous portal heparinization (SCPH) as a therapeutic approach of portal thrombosis after liver transplantation

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Background: Portal thrombosis is a major problem after liver transplantation. Many protocols have been designed in order to avoid and/or prevent it, but, so far, none of them have shown clear advantages.
Aim: To determine the feasibility of portal thrombosis prevention after liver transplantation by continuous portal heparinization.
Material and methods: A 68 year old male patient with a Child B, HCV-related liver cirrhosis and hepatocarcinoma was transplanted at our institution on November 12, 1977. He was an Okuda stage II and preoperative studies did not show any portal thrombosis or other liver transplant contraindications. Preoperative selective chemoembolization was performed. Orthotopic liver transplantation (OLT) with a modified piggyback technique was performed, as we have done in all of our liver transplantations (202). During the hepatectomy, at the moment of portal section, a recent partial thrombosis was found. After thrombectomy, a peroperative histological examination confirmed our impression, excluding a neoplastic origin. Conventional OLT technique was performed and the graft was adequately perfused through the portal vein after usual anastomosis. No other problems were seen. At the end of the procedure, macroscopic findings of portal hypertension were found and a venous catheter (VC) was placed into an ileal branch of the superior mesenteric vein. A peroperatory angiography showed a complete portal thrombosis without any problem from the anastomosis. The VC was left placed and sodium heparin (5000 UI/24 h) was perfused through it. Standard triple therapy immunosuppression was started.
Results: After transient cholestasis, biological data and patient's recovery corresponded to good graft function and a Doppler ultrasonography (DUS) performed 12 hours postoperatively showed a portal permeability with adequate flow patterns. Because of systemic anticoagulation, heparin was changed to subcutaneous low molecular weight (5000 UI/24 h), six days after OLT. A portal angiography by VC showed an adequate portal image of the graft. The VC was removed 15 days after OLT. A new DUS performed 27 days after OLT, showed a good portal flow. The patient progressed well and was discharged on December 12, 1997, 30 days after OLT. Liver pathological findings showed virus C active cirrhosis and hepatocellular carcinoma, major diameter 4·5 cm, in the right lobe without vascular invasion. Chronic, non tumoral, portal thrombosis was also found.
Conclusion: SCPH may be an easy and effective method to manage the portal thrombosis after OLT.

Clinical indications for liver transplantation influence the early acceptance of liver grafts

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Aim: Acute rejection (AR) remains one of the primary complications during first weeks after liver transplantation even using modern immunosuppressive therapies. Different factors in recipients which could affect the immunological acceptance of the graft are analysed in this study.
Material and Methods: Influence in liver graft rejection or acceptance of patient's age, sex, clinical indication for transplant, immunosuppressive therapy (Cyclosporin-A, -CyA-, Conventional vs Neoral), CyA serum-levels and HLA-compatibility, was analysed in 127 recipients.
Results: Clinical indications for liver transplant with the highest AR-rate were Primary Biliary Cirrhosis -CBP- (60 per cent, 9 out of 15), Chronic active hepatitis-C (57 per cent, 16 out of 28) and retransplant (45 per cent, 5 out of 11); in contrast those with the lowest AR rate were Chronic active hepatitis-B (11·1 per cent, 1 out of 9), amyloidosis (12·5 per cent, 1 out of 8), carcinoma (16 per cent, 2 out of 12) and Alcoholic Cirrhosis (27 per cent, 10 out of 26). Histologically confirmed AR-rate in conventional and Neoral CyA treatments were 33·9 per cent (36 out of 106) and 52·4 per cent (11 out of 21). Patient groups treated with CyA-conventional or CyA-Neoral showed similar age and sex distribution, HLA compatibility degree or post-transplant CyA serum-levels. AR was more frequently observed within younger patients (39·9±18 vs 47·2±16 years, P<0·022) and females (53·8 per cent vs 32·6 per cent; P<0·05). The higher number of patients with CBP, retransplant and Chronic active hepatitis-C among women and CyA-Neoral group might explain their higher AR-rate.
Conclusion: Clinical indication for liver transplantation may influence liver-graft acceptance, irrespective of immunosuppressive therapy and donor/recipient HLA compatibility. This fact should be considered especially when AR-rate is studied in small recipient groups.

Chronic rejection in liver transplantation: effect of HLA matching

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Aim: Rejection is still an important problem in liver transplantation and, although different reports show distinct and sometimes contradictory views about the role of histocompatibility in liver rejection, there is evidence that HLA antigens are involved in cellular immune response leading to the rejection process. In this way, this study was carried out to examine the effect of the HLA compatibility between liver transplant donor-receptor pairs and their relationship with chronic rejection apparition.
Material and methods: HLA class I and class II typing was performed following a standard complement dependent microcytotoxicity assay and PCR-SSOP method. One hundred and sixty-five liver transplants were included in this study. Re-transplants were excluded from the analysis. The diagnosis of chronic rejection was based on the conventional clinical and anatomopathological criteria. The relationship between HLA compatibility and the chronic rejection episodes was compared using the X^2 test using an OMS EPI-INFO program.
Results: Analysis was done comparing the compatibility in HLA-A, -B, -DR (serologic) and HLA-DRB1, -DQB1 and -DPB1 with the occurrence of chronic rejection. Only HLA-A compatibility shows statistical significant differences. Among the transplants performed with zero HLA-A matches, the percentage of chronic rejection was 2·8 per cent (3/107), whereas in those with 1 or 2 matches this percentage was 8·5 per cent (4/47) and 75 per cent (3/4), respectively. These differences were statistically significant (P=0·00007).
Conclusion: In summary, the observed results indicate that HLA-A matching could be relevant in the development of chronic rejection in liver transplant recipients.

Long term results of liver transplantation in four siblings from the same family with familial amyloidotic polyneuropathy (FAP) type I TTR Ala-71

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We report the evolution of the polyneuropathy of the extremities and autonomic dysfunction in four sibling patients, from the same family, with the Ala-71 variant treated by liver transplantation (LT). To our knowledge, this is the first world report with this TTR-variant. The specific diagnosis of FAP I was investigated by detection of Ala-71 in serum using the monoclonal antibody FD6 by ELISA technique.

The four siblings are alive from two to five years after LT. After the operation, the seriated determinations of TTR-Ala-71 variant showed a decrease in serum levels in all cases.

In all the patients we noted clinical improvement of the polyneuropathy of the extremities and autonomic dysfunction after LT. However, no patient showed an improvement from the electromyographic point of view. There were a progression of the vitreous amyloid deposits after LT in the three affected patients, likely in relation to TTR synthesis at level of the coroideous plexus. The female patient had a healthy baby 18 months after LT.

In conclusion, the four patients have significantly improved their quality of life after LT.

Life quality and recurrence of alcoholism in alcoholic cirrhosis patients following liver transplant

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Aim: To analyse the life quality and recurrence of alcoholism in alcoholic cirrhosis patients after liver transplant.
Patients and methods: We studied 43 cirrhotic transplant patients divided into two groups, alcoholic cirrhotics (26 cases) and non-alcoholic cirrhotics (17 cases). Life quality was assessed by the Nottingham test, quantification of hospital dependence and rate of return to work. Alcoholic recurrence was assessed by questionnaire, and the alcoholic's post-transplant rate of depression by the Beck test.
Results: 1. The Nottingham test showed a significant improvement ($P<0{\cdot}01$) after transplant in both groups of cirrhotics, with no differences between the two. 2. The sick leave rate after operation decreased with time in both groups, but without significant differences compared to the pre-transplant situation. 3. The alcoholic patients' rate of depression showed an extraordinary post-transplant improvement ($P<0{\cdot}001$). After a mean follow-up of 2 years, only 1 patient (3·8 per cent) presented alcoholism recurrence.
Conclusions: The life quality of alcoholic cirrhotics improves significantly after liver transplant. The recurrence of alcoholism is very infrequent.

Primary cardiac allograft failure after carbon monoxide poisoning

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Introduction: Due to the present organ donor shortage, donor selection criteria are being progressively liberalized. We present a case of carbon monoxide poisoning that led to primary allograft failure. Biventricular assist device was used as a bridge to recovery.
Donor history: The donor heart had been harvested from a 31-year-old woman who died after smoke inhalation in a house fire. The carboxyhemoglobin levels was 36 per cent. After a short period of cardiopulmonary resuscitation and hyperbaric oxygen therapy the carboxyhemoglobin level decreased to 4 per cent with good cardiac function on echocardiography and a normal ECG. Heart, kidneys, liver and pancreas were harvested after brain death.
Receptor history: The receptor was a 62-year-old man with ischemic cardiomyopathy. Orthotopic heart transplantation was performed with an ischemic time of 120 minutes. Weaning from cardiopulmonary bypass (CPB) was unsuccessful despite additional reperfusion, AV pacing, maximal inotropic support and intraaortic balloon counterpulsation. The Abiomed BVS 5000 biventricular assist device (BIVAD) was implanted. Allograft function improved gradually on serial echocardio-graphy within 24 hours after transplantation, although severe mitral regurgitation was noted during weaning. BIVAD explanation was performed on the fifth day. Mitral valve exploration revealed chordal rupture and erosion of the left ventricular wall by the left atrial cannula. A Carpentier Edwards mitral valve was implanted, followed by successful weaning from CPB. Recovery was complicated by Aspergillus pneumonia treated with amphotericin B and itraconazole. Renal insufficiency required temporary hemodialysis. The patient was discharged after 3 months with excellent cardiac function.
Conclusion: 1. Hyperbaric oxygen therapy is an effective treatment for carbon monoxide poisoning, but brain cells and myocytes are extremely vulnerable. Normalization of carboxyhemoglobin level does not implicate immediate full recovery of energy depleted myocytes. Caution is warranted to accept those hearts for transplantation. 2. Primary cardiac allograft failure can be managed by BIVAD implantation as bridge to recovery or to urgent retransplantation. 3. Incorrect cannula placement demands repositioning even with good BIVAD function.

Apoptosis in chronic rejection of human liver allograft

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Introduction: Apoptosis, also called programmed cell death, is one of the most important factor in the pathogenesis of various liver diseases. Apoptosis is presented at low rate in normal human liver as a physiological effect of the liver cell homeostasis and at a higher rate several liver diseases. Two proteins with different activity are of major interest in apoptosis, i.e. FAS/APO-1 located mostly at the surface of hepatocytes and Bcl-2 found at the site of bile ducts. Since chronic liver rejection is characterized by loss of bile ducts (vanishing bile duct), arteriopathy and fibrosis, at least two different pathophysiological aspects can be assumed: T-cell mediated inflammation of epithelium structures and parenchymatosus scaring promoted by macrophages and lipocytes. In order to analyse both presumed pathways, we investigated the expression of FAS/APO-1 and Bcl-2 in comparison with lymphocyte and macrophage distribution in chronic rejected liver allografts.
Material and methods: Biopsy specimens from 10 chronic liver allograft rejection cases were evaluated and compared with eight normal liver controls. TUNEL staining was performed to identify the apoptotic cells. FAS/APO-1 and Bcl-2 expression was assessed using immunohistochemistry. In addition lymphocyte subsets and macrophages were stained (CD3, CD4, CD8, CD20, CD56, 25F9, 27E10).
Results: 1. Increased rate of apoptosis was detected in pericentral hepatocytes and moderate increase in bile duct cells. 2. Bcl-2 expression was markedly upregulated on lymphocytes around the bile ducts, while only few staining of Bcl-2 was visible in pericentral areas and on biliary epithelium in comparison with normal controls. 3. FAS was moderately expressed on pericentral hepatocytes and in bile ducts. 4. T-cells showed dense infiltrat around bile ducts, while B-cells and Nk-cells would not be detected. Conversely macrophages were found only in pericentral areas.
Conclusion: Bcl-2 was downregulated at the site of bile ducts, while increased FAS/APO-1 expression would be demonstrated. These findings suggest an increased apoptosis rate, most likely triggered through the T-cell infiltrate.

Imaging strategy of small bowel Crohn's disease

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Aim: On the basis of our experiences we retrospectively evaluated our patients with small bowel Crohn's disease (SBCD). The purpose of our study was to determine the most efficient diagnostic protocol (enteroclysis, CT, US, immunoscintigraphy) in different stages of the disease.
Material and methods: From 1990 to 1994 we diagnosed SBCD at 144 patients (20 per cent of all patients). We performed enteroclysis and small bowel CT at all patients, abdominal US in almost all patients and in 60 patients 99mTc AgAb immunoscintigraphy. Based on the results of enteroclysis patients were divided into three main groups: early, intermediate and advanced stage of SBCD.
Conclusion: The best protocol in early stage of SBCD is enteroclysis and immunoscintigraphy, CT and US are not necessary. US was effective only if the examination was performed with graded compression (GrUS). CT and GrUS yielded usually positive results if the small bowel wall was thickened. In intermediate and advanced stages all examinations (enteroclysis, CT, US, immunoscintigraphy) showed the pathology. We preferred enteroclysis and small bowel CT to determine the axial involvement and staging of SBCD. GrUS is useful to detect the layers of the bowel wall, the mesenteric proliferation and lymph nodes. With immunoscintigraphy we can identify the areas of the activity of the disease.

Surgical treatment of Meckel's diverticulum

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Aim: We present the results of surgical treatment of Meckel's diverticulum (MD), the most common true diverticulum of the gastrointestinal tract. This is a congenital diverticulum that results from incomplete closure of the omphalomesenteric duct.
Material and methods: During the period 1993–1997 a total of 21 patients with MD were surgically treated in our hospital. These have been retrospectively analysed.
Results: There were 13 (61·9 per cent) clinically symptomatic MD and 8 (38·1 per cent) asymptomatic MD, found incidentally at laparotomy. Complications of MD included intestinal obstruction in eight, acute diverticulitis in four and peptic ulcer in one case. Resection of the segment of ileum bearing the diverticulum was performed in 14 cases and resection of the diverticulum in two cases. Ectopic gastric mucosa, large bowel mucosa, pancreatic tissue and neoplasms were verified on histopathological biopsy. Wound infection as complication were found in two cases. Mortality was 0 per cent.
Conclusions: Treatment of symptomatic MD is by intestinal resection and end-to-end anastomosis in one layer. Asymptomatic MD requires no treatment in adults. Segmental ileal resection (if the base is wide) or prophylactic diverticulectomy (if the base is narrow) is required for prevention of diverticular disease in childhood.

The incidence and results of treatment in case of bleeding and perforative gastroduodenal ulcer

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Introduction: The bleeding and perforated gastroduodenal ulcer is still a significant problem in emergency surgical practice and the incidence of these pathologies has not decreased during the last five years.
Aim: To evaluate the results of treatment in cases of bleeding and perforated gastroduodenal ulcer and demonstrate the main causes.
Material and methods: From 1993–1997 378 patients with a diagnosis of bleeding and perforated gastroduodenal ulcer were admitted to our clinic. Main causes of bleeding and perforation, methods of treatment, complications and mortality were investigated during retrospective research.
Results: 332 (87 per cent) patients with bleeding gastroduodenal ulcer and 46 (13 per cent) with perforated gastroduodenal ulcer were admitted. The majority of patients did not receive adequate conservative medication. In some cases this complication was the first manifestation of ulcer disease. Within the bleeding group (n=332) 133 (40 per cent) of patients were operated on. Within the perforated group we operated on all patients (n=46). In case of perforation 4 (9 per cent) gastric resections, 11 (24 per cent) vagotomies + pyloroplastics and 31 (67 per cent) simple suture procedures were performed. Within the bleeding group, 1 duodenal fistula and two deaths occurred; 96 (72 per cent) operations in the bleeding group were oversewing of the bleeding vessel and 37 (28 per cent) gastric resections.
Conclusions: The most significant treatment for decreasing ulcer disease complications is adequate conservative treatment. An operation may be the method of choice for patients unable to receive the adequate conservative treatment for social reasons.

Secondary mesenteric venous thrombosis due to apparent polycythaemia

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Introduction: Mesenteric venous thrombosis is a rare pathological condition due to multiple aetiologies as: inflammatory or infectious conditions, surgical trauma, portal hypertension or hypercoagulability status (such as neoplasia, polycythaemia, contraceptives, thrombocytosis, Antithrombine III deficiency, Protein C or S, or myeloproliferative conditions).
Clinical case: A 27 year old male was admitted with severe, diffuse abdominal pain, vomiting, bloody stools for 48 hours. Exmorbidly obese (he weighed 200 kg and had surgery four years before), heavy smoker (three packs a day). He had, during the last year, four episodes of bloody liquid diarrhoea. He was admitted with polyglobulia (hematocrit 66 per cent, Hgb 21 per cent and Quick 42 per cent). Simple abdominal X-rays shows small bowel dilation, leucocytosis, Hematocrit of 50 per cent and Haemoglobin of 19 gr. At surgery a necrosis of the terminal ileum and caecum was found and a right hemicolectomy was done. He had a good postoperative course. Three months later, determinations of Antithrombin III, Protein C and S, PCA resistance were normal. The erythrocyte mass was normal at 29 ml/kg and so was the Carboxyhaemoglobin of 7·8 per cent. The patient stopped smoking, and is now asymptomatic and has normal hematocrit one year after surgery.
Discussion: The term 'apparent polycythaemia' is applied to a group of patients with elevated hematocrit (over 51 per cent in males and 48 per cent in females) with abnormal erythrocyte mass (below 35 ml/kg in males and 32 ml/kg in females) which is the difference from real polycythaemia. It is common in young males. It is associated with smoking and arterial hypertension and also with obesity, heavy alcohol intake, and diuretic therapy and to hypoxemia.

Burge reports an increase in the incidence of occlusive disease in polycythaemia six times over the expected and Weireb had a high incidence of 30 per cent of thromboembolic complications in these patients. Measured cerebral flow in polycythaemia apparent and vera, has an inverse correlation with the hematocrit. The first step in the treatment is to reverse the risk factors once discovered. If the hematocrit is over 54 per cent, blood drawing and replacement with saline should be done.

Duodenal switch with or without pyloroplasty in the treatment of alkaline reflux gastritis: our experience

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Postbulbar total duodenal diversion (PTDD) can be used in the treatment of primary duodenogastric reflux with superior physiologic consequences compared with classic Roux-en-Y.

The procedure consists of a pancreaticobiliary diversion with a small segment of suprapapillary duodenum left in continuity with the stomach to avoid the disruption of the hormonal interplays between duodenal mucosa and gastric compartment in response to acidification of duodenal environment. The suprapapillary duodenum is divided using a TA stapler; a conventional Roux-en-Y is created with minimal dissection of the mesentery to avoid interruption of nerve supply to the bowel. The distal jejunal segment is brought through transverse mesocolon and end-to-end duodenal anastomosis is achieved; end-to-side jejunojejunal anastomosis is carried out at a distance of 50 cm. An extra-mucosal pyloroplasty according to Heinecke-Mikulicz is facultative. The clinical preoperative evaluation of patients consists of: (a) endoscopic demonstration of alkaline gastritis with evidence of bile pooling and pathologic confirmation; (b) 24-hour gastric pH recording; (c) radionuclide 99mTc scanning; (d) radionuclide gastric emptying study or US emptying time evaluation.

We carried out the duodenal switch procedure in 12 patients aged between 26 and 70, all with symptoms of nausea, persistent vomiting and epigastric pain: five had alkaline gastrooesophageal reflux and they underwent PTDD together with antireflux Nissen procedure; one patient had previous Nissen operation without symptoms relief; the remaining six patients were affected with primary alkaline gastritis alone. A pyloroplasty was also performed in two patients to ensure adequate gastric emptying time.

The follow-up (endoscopy with pathologic specimens, barium radiographs, radionuclide gastric emptying study) found the duodenal switch operation of value in the treatment of duodenogastric reflux without inducing delayed gastric emptying if surgical management is entertained in patients selected by accurate preoperative study.

Bronchial carcinoma metastatic to gastrointestinal tract and abdominal wall: report of two cases and review of the literature

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Aim: The authors report two rare cases of metastases from bronchial cancer, respectively in a jejunoileal loop, causing intestinal obstruction, and in the right inferior quadrant of the abdominal wall. The aim of the study was the evaluation of the incidence of gastrointestinal metastases from lung carcinoma in the literature, the relative outcome and prognosis. The authors also analyse the role of the surgical treatment and the prognostic factors in these patients.

Material and methods: Two cases of metastases from bronchial carcinoma were observed. In case 1 a jejunoileal obstruction secondary to metastases from lung adenocarcinoma in a male of 69 years, already submitted to radio-chemiotherapy for inoperable adenocarcinoma of the right lung, was observed. The patient underwent jejunoileal resection and right hemicolectomy and recovered fully. In case 2 a large abdominal parietal mass involving the third inferior part of the right rectus muscle in a 64 year old female with undiagnosed squamous cancer of the left lung was observed. Preoperatively it was misdiagnosed as an ovarian neoplasm. The patient was operated on with an explorative laparotomy and resection of the metastasis 'en bloc' with a large part of the inferior right quadrant of the abdominal wall. After the operation the patient underwent six cycles of chemo-radiotherapy for her lung cancer.

Results: The surgical outcome was free of specific complications in each case. Patient 1 died from neoplastic cachexia four months after the operation, while patient 2 is still alive and undergoing scheme of radiochemotherapy, six months after surgery, with partial reduction of the pulmonary mass.

Conclusions: According to the latest reports in the literature, the authors conclude that the metastases of gastrointestinal tract from bronchial cancer are very rare. In every case they represent a terminal compromise of the immune system and so the prognosis is very poor. The appropriate role of surgery is to prevent or to treat the relative complications such as intestinal obstruction or perforation.

High incidence of duodenal ulcer perforation in North-African migrants

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Introduction: We studied the incidence and morbidity-mortality of duodenal ulcer perforation in native Spanish people and in North-African migrants. Peptic ulcer perforation is a stress-related situation in many studies.

Patients and method: Between October 1991 to April 1997, 155 patients were operated on because of peptic ulcer perforation. One hundred and twenty-six were Spanish, 25 North-African migrants, two European tourists, one Chinese cook and one Bulgarian truck-driver. These last four patients were excluded from study. We compared the incidence of perforated ulcer in Spanish and migrant populations, and morbidity factors associated with surgery. The migrants were Group I. We selected all Spanish males under 50 years of age for Group II. Statistical analysis were carried on SPSS and Epitable programs.

Results: Spanish people incidence was 7 cases/100 000 hab. /y., Group I (North-African migrants) incidence was 45·45 cases/100 000 hab. /y and Group II (selected Spanish) incidence was 10·8 cases/100 000 hab. /y. ($P<0{\cdot}001$). Sex distribution was 103 males (81·7 per cent), 23 females (18·3 per cent). All migrant patients were males. Mean age was 47·13 years (13–94), Group I was 30·92±7·85 years, and Group II 32·14±9·7 years ($P=0{\cdot}09$). Mean hospital stage was 11·19±7·5 days, 9·56±5·18 for Group I, and 10·19±8·04 days for Group II ($P=0{\cdot}33$). Peptic antecedents were similar for Group I (52 per cent) and Group II (57·1 per cent; $P=0{\cdot}6$), but other antecedents were higher in Group II (41 per cent) than in Group I (8 per cent; $P=0{\cdot}002$). Surgery was truncal vagotomy plus pyloroplasty 96 per cent in Group I, 91 per cent in Group II ($P=0{\cdot}7$), and 81 per cent for the whole series. Morbidity was 29·36 per cent for the complete series, 12 per cent for Group I and 21·4 per cent for Group II ($P=0{\cdot}39$). Mortality was 5 cases (3·9 per cent).

Conclusions: Peptic ulcer perforation was more frequent in migrant people than in the Spanish population, with statistical significance. Hospital stage and morbidity are comparable between migrants and sex and age related Spanish group. Nutrition, personal, work, social and political situations probably are responsible for the high incidence of peptic ulcer perforations.

Primary and secondary neoplasms of the small bowel and their complications (single centre study)

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Introduction: The incidence of small bowel tumours is not accurately defined, the data of different authors showed that they present 0·5–5 per cent of gastrointestinal neoplasms. These tumours are difficult to find by conventional diagnostic procedures.

Aim: to analyse the data of the patients with small bowel tumours during the first four year period of our Institute.

Material and methods: From January 1994 until January 1998 at our department eight patients were treated for small bowel neoplasms. There were six men, average age 46 years and two women, average age 74 years; main hospital stay was 14 days. The following diagnostic investigations were used to find the tumours: abdominal ultrasonography, barium contrast radiography, endoscopy, selective enterography, CT, angiography. The data were analysed retrospectively.

Results: Symptoms associated with the tumours include epigastric discomfort, intermittent abdominal pain, weight loss, palpable abdominal mass, small bowel obstruction and bleeding. The preoperative investigation was successful in five cases. Three of these tumours were found in the jejunum and five of them in the ileum. In three cases acute surgery was necessary because of bleeding and obstruction, in five cases elective operation was performed. Resection of the small bowel was carried out in seven cases, and right hemicolectomy was chosen for oncological reasons in three cases. A malignant tumour of the jejunum was considered not removable surgically, a palliative gastro-enterostomy was performed.

The histological examination showed one leiomyoma, one benign neuromuscular tumour, two malignant carcinoid, one Non-Hodgkin lymphoma, one adenocarcinoma as primary neoplasms and two metastases of malignant melanoma as secondary tumours. On one patient with carcinoid tumour of the ileum – after the resection and chemotherapy– a successful orthotopic liver transplantation was performed because of multiple liver metastases. There were no perioperative complications, we lost two patients (one malignant melanoma, one lymphoma) six months later.

Conclusions: Neoplasms of the small bowel are extremely rare and the symptoms are often vague, the tumours are discovered – in a considerable proportion – too late. Probably for this reason the five year survival rate is about 30–40 per cent. The small bowel tumours always represent a diagnostical and therapeutical challenge for the surgeon.

Anal Canal

A modified Core Out fistulectomy

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Aim: To evaluate results of a modified Core Out fistulectomy with a surgical internal sphincter saving dissection and separate layer closure of the sphincters in high and low (in women) transphincteric fistulas.
Patients and methods: Ten patients have been operated on by this technique during the last two years. None had been operated on due to fistula previously. All of them presented with transphincteric fistulas (Park's classification). An incontinence questionnaire (Pescatory scale) was done preoperatively and at three, six months and yearly postoperatively. All patients were prepared the day before surgery with Polyethylenglycol 3–5 l. Surgery was done in lithotomy position in nine cases and endoanal exploration was realized with the Park's retractor. Surgical technique consisted in fistulous tract dissection from the external orifice through the sphincter layers to the internal one. Afterwards a separated layer closure beginning with the internal sphincter was done with absorbable suture. An endorectal mucosa advancement flap was fixed to the internal sphincter in six cases and a vertical simple mucosa suture in four. Wound care was done from the first postoperative day on and weekly postoperative controls until complete healing.
Results: Ten patients (seven male/three female) with a mean age of 38·87 (R: 24–55) were operated on due to anal fistula. The mean wound healing time was between 28–50 days. There were two dehiscences from the advancement flap plasty and two with the vertical suture. None of the endorectal advancement flap dehiscence developed a recurrent fistula. One of the vertical suture dehiscence manifested due to several light rectal bleeding episodes which stopped after spontaneous healing. The other one needed a very superficial sphincterotomy. One case developed a recurrent fistula (10 per cent). Postoperative follow-up was minimum three months and maximum 28 months. Postoperative ultrasound (n=3) revealed images of internal sphincterotomy. No incontinence was seen.
Conclusions: Transphincteric fistulectomy uncutting the internal sphincter allows excision of the fistulous tract in a most preserving sphincter dissection and may be an alternative option in selected cases instead of the classical Seton technique for transphincteric fistulas.

Endoanal ultrasound in evaluation of anal fistula

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Aim: To evaluate the accuracy of endoanal ultrasound in cases of anal fistula.
Material and methods: We performed endoanal ultrasound to study 38 patients with anal fistula, six of them with recurrent fistula. The patients were in left lateral decubitus position. We used an endorectal ultrasound probe 7·5 MHz, sectoral of 120° with possibility of rotation to 360°, to evaluate the anal sphincters, levator anus muscle, supralevator and ischiorectal spaces and the fistula tracts. We enhanced the fistula tract image by instilation of hydrogen peroxide.
Summary: The diagnoses were: intersphincteric fistula in 20 patients, trans-sphincteric in 10, suprasphincteric in four and subcutaneous in four. The exam was well tolerated and we had a perioperative confirmation of all the ultrasound diagnosis.
Conclusion: Endoanal ultrasound showed to be a well tolerated exam with brief execution and good accuracy in the preoperative classification of fistula tracts, allowing the selection of anaesthesia and surgical procedures.

Efficacy of anal stretch and lateral sphincterotomy in treating children with chronic anal fissures

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Background: A recent study advocated lateral sphincterotomy as treatment of choice for children with chronic anal fissures (Br. J. Surgery 1995; 82: 1341–1342). However, this was disputed in subsequent correspondence (Br. J. Surgery 1996; 83: pages 442 and 571–572). The aim of this study was to evaluate the efficacy of two commonly performed procedures for treatment of chronic anal fissures in children.
Methods: A retrospective analysis of children documented as having a chronic anal fissure treated by anal stretch or lateral sphincterotomy using a surgical log book held by one of the authors (MDS). All procedures were performed by a single surgeon using standard techniques.
Results: Twenty-seven procedures on 21 patients aged between seven months and 9·5 years (18 of 21 less than three years of age) were carried out over a four year period between 1992 and 1996. Twelve of 16 patients undergoing lateral sphincterotomy had healed by eight weeks (including three children who failed to heal following anal stretch) compared with three of 10 patients undergoing anal stretch (11 procedures) $P<0{\cdot}02$.
Conclusions: Lateral sphincterotomy is more effective than anal stretch in treating children with chronic anal fissures. Long-term follow-up studies are required to ensure we are not predisposing these children to faecal incontinence in adult life.

Anal keratoacanthoma – difficult diagnosis, easy therapy: three case reports

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A keratoacanthoma is a rapidly growing tumour, usually occurring on sun exposed areas of the skin. It invades the dermis, but remains local and can resolve spontaneously. Keratoacanthomas, however, are rare in the anal region. To our knowledge only two keratoacanthomas in the anal region are described in the literature. Clinically, but also histologically, this tumour may mimic an anal carcinoma. Three male patients, who were 58, 63 and 64 years of age, presented with a perianal tumour. None of the patients had had a transplantation or were on immunosuppression therapy. Macroscopically the differential diagnosis of an anal carcinoma was made. The tumours were excised. The pathologist could only make the diagnosis of a keratoacanthoma with the additional knowledge of the short history of the tumour (6–10 weeks). The history, clinical appearance, therapy, pathology, follow-up and prognosis of these patients with this rare anal tumour are demonstrated. After securing the diagnosis no further therapy for the anal keratoacanthoma is needed.

Anal endosonography is a useful diagnostic tool in anal fistulas and anal abscesses

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Anorectal endosonography is a new technique, which permits preoperative diagnosis and classification of anorectal abscesses and fistulas. With instillation of hydrogen peroxide blind ending fistula tracks and complex fistula systems may be visualized. The correct anatomical classification of fistulas and abscesses in relation to the anal sphincter may be decisive for the operative treatment. Until recently, the exact course of an anal fistula could be demonstrated only at operation by laying open the fistulous tract. X-ray contrast studies gave only evidence of possible fistulous side tracts and extensions into the rectum without representing their relation to the sphincter system. With anal endosonography it is possible to directly visualize the lesions caused by fistulas and abscesses in relation to the anal sphincter muscles. We want to report our endosonographic experiences with 81 patients with anal fistulas and/or abscesses. In 89 per cent of the fistulas and 100 per cent of the abscesses a correct preoperative diagnosis according to the Park's classification was made by endosonography. Anal endosonography therefore is a suitable and helpful diagnostic tool in the diagnosis of anal fistulas and abscesses, non-invasive, easy to perform and relatively inexpensive.

Results of surgical treatment for differentiated thyroid carcinoma

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Aim: To evaluate the early and late results of our therapeutic approach in patients with differentiated thyroid carcinoma, which is strongly related to the stage of the disease and to the risk group of the patients.
Material and methods: Records of 134 unselected patients with differentiated thyroid carcinoma operated from 1971 to 1997 were retrospectively analysed. The histologic type of carcinoma was: folicular in 46 patients (34·33 per cent of cases), papiary in 45 patients (33·58 per cent of cases) and mixed papillary and folicular in 43 patients (32·09 per cent of cases). In the low risk group (AMES criteria) there was 88 patients (65·6 per cent of cases): near total lobectomy on the side of the lesion and subtotal lobectomy on the contralateral side was done. The high risk group includes 46 patients (34·33 per cent of cases); total lobectomy on the side of tumour and contralateral subtotal or near total lobectomy was the operation of choice. Thyroid suppression and radioactive iodine were added. The postoperative morbidity rate was 23·88 per cent (32 patients) and the postoperative mortality rate was 3·73 per cent (five patients). The 10 year survival rate was 95·45 per cent (84 cases) in the low risk group of patients and 62·79 per cent (27 cases) in the high risk group. The recurrence rate of the disease was 6·72 per cent (nine patients). The tumoral antigenic markers were evaluated periodically; also sonographical assessments of the remaining thyroid was done.
Conclusion: These data indicate that this quite conservative surgical approach used at our institution has similar results to more extensive surgical treatment used in other institutions.

Our experience in aesthetic rhinoplasty: study made on 500 operated cases

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Introduction: The nose plays a very important role in defining one's facial aspect and this was – beside its central position on the face – the main reason for Lavater to call it 'the keystone of the face'. The shape of the nose does also involve some character features. These would be just a few of the reasons confirming the necessity of performing rhinoplasty.
Material and methods: Here is presented a retrospective view of the 500 operated patients in seven years – 435 females and 65 males. The age of the patients varied within the limits of 16 and 47 years. In 355 of the cases we were confronted with constitutional deformities, the other 145 being performed on post-traumatic or postoperative deformities.

In all the operated cases, the surgeon had to consider patients' motivation, considered as sufficient and real when it showed up as the result of a long duration acknowledgement of the defect by the patients, involving psychological and character problems.

In order for the best aspect to be achieved it has to be performed in the preoperative stage (for the great majority of the patients) a photographic or computer based analysis of the potential result, ending in choosing – with the patient's consent – the best variant.

Technically, in 472 cases it was performed a closed rhinoplasty, the open rhinoplasty being chosen only for a few post-traumatic deformities. In 15 of the cases a silastic prostheses was used.
Results: In appreciating the results we mainly took into account the patient's degree of satisfaction with them. And so for 400 of the patients (80 per cent) the result was a very satisfactory one, for the other 100 (20 per cent) it was just good. From these 100 patients, 28 of them (5·6 per cent) needed further surgery.
Conclusions: 1. Any aesthetic surgery intervention's guiding line is to make the patient look better; 2. The aesthetic surgery of the nose helps the patient in his instinctive need for correcting existing deformities; 3. The estimation of the result by the use of photographic methods and computer software substantially increases the intervention's rate of success.

Three dimensional CT-reconstruction in patients with atlanto-axial rotary fixation

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Aim: Patients with suspected atlanto-axial rotary fixation are in some instances difficult to diagnose properly without using computed tomography. In our hospital three dimensional reconstruction of CT examinations have been used routinely when evaluating such patients thereby obtaining valuable diagnostic information. The aim of our presentation is to describe the method used and how it may be applied.
Material and methods: We present a ten year old girl who suffered a neck trauma when hitting the bottom of a swimming pool while diving. Severe neck pain occurred immediately. After a short period of time her neck became 'stiff', rotated and fixed in flexion. Clinical examination and conventional radiograms were inconclusive, but fracture was suspected. Standard CT examination did not offer any conclusion, but spatial CT with three dimensional reconstruction revealed an atlanto-axial rotary fixation.

The examinations were performed using a Phillips Tomoscan SR 7000. Field of view (FOV) was set to 110 using 250 mAs and 120 kV. For the reconstruction FOV was adjusted to area of interests and the reconstruction index was set to 1 mm.
Conclusion: A proper treatment of atlanto-axial rotary fixation requires an exact and early diagnosis. As both clinical, conventional radiographic and standard CT examinations may be inconclusive, we strongly recommend to examine these patients with three dimensional CT-reconstruction to obtain a best possible graphic picture of the anatomic conditions.

Chemodectomas diagnosis and localization: advantages of 111In-pentetreotide over 123I-MIBG scintigraphy

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Aim: Chemodectomas or Glomus tumours are unusual head and neck paragangliomas. The non-invasive imaging technique metaiodobenzylguanidine (MIBG) scintigraphy has been used for the diagnosis of all types of paragangliomas during years. The purpose of this study is to evaluate and to compare the classic 123I-MIBG scintigraphy and the recent 111In-pentetreotide scintigraphy in the diagnosis and localization of chemodectomas or glomus tumours.
Material and Methods: In order to get it, we have performed 123I-MIBG and 111In-pentetrotide scintigraphy in eight patients (seven women and one man) with histologic or radiologic confirmation of chemodectoma (five carotid body and three yugolotympanic chemodectomas).
Results: 123I-MIBG uptake were visualized in four patients on planar views and SPECT images (sensitivity 50 per cent, 4/8), and uptake was low to moderate in all patients. Using 111In-pentetreotide scintigraphy all chemodectomas of our eight patients were visualized (sensitivity 100 per cent, 8/8), and 111-In-pentetreotide uptake intensity was high in all cases.
Conclusions: In conclusion, this study indicates that 111In-pentetreotide scintigraphy is superior to 123I-MIBG scintigraphy in diagnosis and localization of chemodectomas or Glomus tumours. Moreover, 111In-pentetreotide scintigraphy permits a good classification of patients with or without somatostatin receptors in the chemodectoma in order to intend a pharmacological therapy with somatostatin analogues in inoperable tumours.

Programme of major surgery with minimal hospital stay: assessment after one year under development

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Aim: Surgery involving the minimal hospital stay offers evident advantages to the patient and hospital. The results obtained in a programme of major surgery in which the hospital stay was 24 hours or less are presented after one year of development.

Material and methods: Between January to December 1997 a total of 4806 patients were operated in our hospital. Fifty-two vascular procedures, 210 urological, gynecological 6, ophthalmic 870, ear nose and throat 735, general surgery 876, procedures and minor procedures 2057.

The basis of our programme involved those patients with a requirement of about 24 hours hospitalization or less (F.E. laparoscopy in biliar pathology).

Results: In relation with our admission criteria a high percentage of our patients were out in the same day. 4115 patients (85·58 per cent) were out the same day and 691 (14·32 per cent) stayed more than 24 hours, in general for minor complications (pain, general disorders, etc) or geographical factors. No problems were observed in patients review in gynecological procedures, four arterio-venous fistula were occluded and needed a second operation. Ophthalmic patients (cataract mostly) were out in the same day with no problems. ENT patients required hospital stay, 35 cases for bleeding. In general surgery most of patients were operated on in the afternoon and were out at the following day in the morning with less than 24 hours stay. We observed five recurrences in groin hernia operated on without protheses.

Conclusion: We consider that AM surgery in our unit has improved quality of life.

Advantages of one day surgery in proctological practice

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In the last seven years the authors have safely operated on 640 patients in the out-patients department, all for proctological diseases under local, regional and caudal peridural anesthesia. These included 396 haemorrhoidectomies (Morgan-Milligan procedure), 25 lateral internal sphincterotomies and 88 anal stretches for fissures, 56 transsphincteric fistulas (silk thread, elastic ligatures), 45 ischiorectal abscesses (drainage, silk thread), 32 rectal prolapses (Delorme-Rehm + Tiersch plastic with wire). After observation, 5·3±0·5 hours, on the same day patients were discharged home, but a surgeon was on call. Only 4·4 per cent, 25, of operated patients had some problems in the first 24 hours, bleeding, pain, discharge, retention of urine. All patients were checked after 3, 7 and 14 days. 79·5 per cent from 452 patients were operated under caudal peridural anestesia, 20cc of 0·5 perc. Marcain, with optimum and satisfactory analgesia, the rest under local infiltration Lidocaine 0·5 perc. and Adrenaline 1:200000. Postoperative pain was reduced with long acting analgesia combined with non steroid anti-inflammatory drugs with excellent results.

Most proctological diseases can be operated on and treated as one day surgery cases under safe and effective caudal peridural anaestesia which gives a guarantee of 5 to 8 painless postoperative hours. The reduction of the hospital stay of patients treated surgically for proctology is an attractive alternative that lowers cost without increasing morbidity.

Aesthetic one day surgery

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The presented materials includes 228 patients operated on for aesthetic purposes only in the outpatient clinic of plastic surgery within the years 1993 to 1997. One day surgery is preferred there, on account of considerably reduced total costs of treatment. The age of the patients ranged from 5 to 68 years.

The most frequent indications were nonaesthetic scars (63 patients – 27·6 per cent). The other were: prominent ears (60 patients – 26·3 per cent), nasal deformities (36 patients – 15·7 per cent), different kinds of mammaplastics (24 patients – 10·5 per cent).

Most patients were operated on under local anaesthesia (143 patients – 62·7 per cent). General anaesthesia was delivered in more extending surgical procedures and in children.

The majority of patients were treated in the ambulatory setting. Those, who underwent operation under general anaesthesia were usually discharged home two hours after operation. Only a few of them (11 patients – 4·8 per cent) were admitted for two or three days. It depended on the extent of operation procedure. All these patients received antibiotics i.v. in bolus at the beginning of the operation. In some cases of PONV (postoperative nausea and vomiting) Zofran 4 mg i.v. was administered in single dose.

In general, the complication rate was rather low and did not exceed 4 per cent of cases. According to the simple scale worked out by us a few years ago, we have obtained more than 90 per cent of very good and good results.

In our opinion, existence of one day surgery depends on good organisation and cooperation between surgeon and anaesthetist.

Major ambulatory surgery: organization and results after one year of experience

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The creation of Units of Major Ambulatory Surgery has become necessary to compensate the increased number of surgical patients in waiting lists and to reduce costs without decreasing the quality of the assistance. In this study we analysed the structure, arrangement and results of our Department of Major Ambulatory Surgery after one year of experience. A total of 2241 surgical procedures was performed by the different specialities: Ophthalmology 980, General and Digestive Surgery 393 (Proctology and Abdominal wall), Otorhinolaryngology 384, Orthopedic Surgery 38, Gynecology 69, Plastic Surgery 286, Urology 52, Stomatology 21, Others 5. The mean duration of the procedures was 54 minutes and the mean time needed for recovery oscilated from 10 to 49 minutes. Retobulbar anesthesia was used in 960 cases, general in 754, local with sedation in 270, and subarachnoidal in 93. There was a minimum percentage of epidural anesthesias and local anesthesia was used in the rest of cases. The rate of complications was very low, with 2 per cent of admissions, 0 per cent of readmissions, 3 per cent of emergency aids and 4 per cent of telephone calls. The degree of patient satisfaction was very good in 55 per cent of cases and good in 35 per cent.

Conclusions: Major Ambulatory Surgery performed in Units specially designed for it is a fast and viable method in our system. We think that this constitutes the method of choice for the surgical treatment of a great variety of pathologies due to its low cost, few complications and the high level of participation of the different surgical specialities as well as the great patient acceptance.

Day surgery anaesthesia

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In the USA more than 50 per cent of the surgery interventions are thought to be feasible in Day Hospital. In Italy ambulatory surgery is undergoing an important development owing to the introduction of surgery methods less and less invasive and to the adoption of Local Regional Anaesthesia (LRA) as alternative to the General Anaesthesia (GA).

Advantages of LRA: 1. Patient quick autonomy; 2. Nausea and vomiting absence; 3. Satisfying analgesia in the post-intervention; 4. Early nourishment. Disadvantages: 1. Headache; 2. Retention of urine; 3. Orthostatic hypotension. In our DH-Department the following interventions have been carried out: nr. 330 in Superselective Spinal Anaesthesia (SSA), nr. 24 in Plexis Anaesthesia (PA), nr. 170 in Local Anaesthesia + Sedation (LA+S).

All the patients are classified as ASA 1 and ASA 2, aged between 16 and 82 years old, average 42. During the intervention the PA, ECG, and SaO2 are monitored. The SSA has been adopted for varix surgery and for athroscopy, being a less traumatic method and for the scanty hemodynamic pertubation involved, considering the limited extension of the sympathetic block. For nerve isolation the neurostimulator is employed to help to block the brachial plexus. In inguinal hernia surgery the LA+S has been adopted, using Xylocaine and Midazolam. During the interventions in case of hypotension over 20 per cent of the base value, reduced quantities of α stimulating drugs are given, avoiding filling. In one case in LA+S a severe crisis of broncho-spasm occurred, which was resolved by using broncho-dilatators and O2.

Adopted criterions for discharge: 1. Full restoration of the conscience after sedation; 2. Nausea and vomiting absence; 3. Spontaneous return of diuresis; 4. Absence of sympathetic blockage. All the patients are dismissed within four hours of the intervention. During the checking in the sixth day no one patient reported complications connected to the anaesthesiology method. The LA is the most suitable method for the ambulatory surgery because it allows for a rapid dismissal with scanty or null complications.

Extra-corporeal methods of detoxification and immunomodulation in the management of acute purulent mediastinitis

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Aim: Acute purulent mediastinitis is characterized by significant endotoxaemia and often associated with immune deficiency, necessitating an adjuvant treatment aimed at detoxification and immunomodulation. The purpose of the study was to compare the detoxification and immunomodulating effects of four different methods: haemoperfusion (HP), plasmaphoresis (PS), extra corporeal irradiation of autologous blood with laser (LI) and ultraviolet light (UVI) in the treatment of this inflammatory condition.
Material and methods: 31 patients (19 men, 12 women; median age 43 years, range 17 to 61 years) suffering with acute purulent mediastinitis of various aetiology were divided into four groups according to the employed method of detoxification and immunomodulation: HP (7 patients), EP (8 patients), LI (8 patients) and UVI (8 patients). All procedures were carried out only after surgical drainage of the primary focus of inflammation. Effects were assessed before and on the first day after the procedure by measuring the level of endotoxaemia (serum mean molecular weight peptides), certain parameters of antibody (serum Ig A, G, M) and cell-mediated immunity (T lymphocyte and active T lymphocyte count) and phagocytic activity of neutrophils and monocytes.
Results: HP had the maximum detoxificating effect, slightly stimulated antibody-mediated immunity but suppressed cell-mediated immunity and phagocytosis. PS also had the detoxificating effect, though inferior to that of HP, and caused deterioration of all measured immunological parameters. Both LI and UVI had no detoxification properties but stimulated antibody and cell-mediated immunity and phagocytosis. The immunomodulating effect of LI was found to be superior to that of UVI.
Conclusion: HP and PS could achieve effective detoxification but had the undesirable side-effect of immunosuppression. Conversely, LI and UVI did not influence the existing endotoxaemia but showed the immunostimulating effect. In order to overcome the side-effect of HP and PS, it might be beneficial to use these methods in combination with LI and/or UVI.

Efficacy of Piperacillin/Tazobactam in intra-abdominal infections

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Introduction: Most intra-abdominal infections are usually polymicrobial. The treatment requires surgical intervention together with antibiotic therapy against aerobes and anaerobes. Piperacillin is a potent antimicrobial proven to be active against a broad range of gram-negative pathogens. The combination with Tazobactam (potent betalactamasa inhibitor) is particularly promising for use in these infections.
Aim: To compare the safety and the clinical-microbiological efficacy of Piperacillin/Tazobactam vs Cefotaxima plus metronidazole in intra-abdominal infections.
Material and methods: Eighty adult patients with documented intra-abdominal infections for peritonitis, intra-abdominal abscess, complicated appendicitis or diverticulitis and cholecystitis requiring laparotomy were enrolled. Forty patients were treated with Piperacillin 4 g/Tazobactam 500 mg every 8 hours and 40 patients with cefotaxima 1 g plus metronidazole 500 mg every 8 hours. We compared clinical and bacteriological efficacy, tolerance and adverse effects.
Results: A 95 per cent (38/40) favourable response (cured/improved) was demonstrated in the group treatment with Piperacillin/Tazobactam and 82 per cent (33/40) with cefotaxima plus metronidazole. The eradication rate in patients at early and late follow-up evaluation was 90 per cent with Piperacillin/Tazobactam and 88 per cent with the second group. The incidence of adverse effects in the group treated with Piperacillin/Tazobactam was five patients (12·5 per cent) and seven patients (17·5 per cent) in the other group. The rest of parameters were not significantly different.
Conclusions: Results of the present study show that Piperacillin/Tazobactam is effective for monotherapy of intra-abdominal infections and it represents a safe alternative as empirical therapy in peritonitis.

Postsurgical infections in bariatric surgery using gastric bandage

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Postsurgical infection (PI) rates have been clearly reduced by adopting laparoscopic procedures. In open bariatric surgery postoperative complications such as surgical wound infections or respiratory (RTI) and/or urinary tract infections (UTI), were quite frequent. Moreover, the obesity is an outstanding risk factor that significantly increases the postsurgical infection rates in most surgical procedures. Laparoscopic surgery, minimizing the length of surgical incision and allowing an earlier postoperative mobilization of the patient, would play a favourable role in decreasing postoperative complications also in bariatric surgery. A brief analysis of our data is reported here, regarding 49 consecutive patients in which a laparoscopic gastric bandage was carried out in the last three years.
Material and methods: From March 1995 to December 1997 49 obese patients were submitted to laparoscopic adjustable gastric banding, as firstly described by Kuzmack (1990). Among them 15 were males (30 per cent) and 34 were females (70 per cent). The mean age was 37 years (SD 9), ranging from 18 to 60 years. The mean preoperative BMI was 46·3±5·4. In five patients laparoscopic procedure was converted to open procedure (10 per cent). The mean surgical time was 120 minutes, ranging from 90 to 180 minutes. In open procedures it was of 150 minutes and in laparoscopic procedure it was of 120 minutes. Perioperative antibiotic prophylaxis was adopted in every patient, using a long acting cephalosporin (Ceftriaxone). The mean length of postoperative hospitalization was five days, ranging from four to seven days. In the early postoperative period only two PI were recorded: one SWI recorded and one RTI. Neither intra-abdominal nor UTI were observed. The mean follow-up was 19 months and no late postsurgical complications were detected or referred by the patients.
Conclusions: A PI rate of 4 per cent compares favourably to our previous experience in open surgery: seven (14 per cent) PI were scored in 51 patients submitted to gastric bandage and 23 PI (16 per cent) were detected in 146 patients submitted to gastric bypass. It seems reasonable to confirm laparoscopic gastric bandage should be considered as gold standard for surgical treatment of the morbid obesity, in suitable patients.

Specificity of catheter related bacteremias (CRB) development in intensive care units with surgical profile

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Objective: To study the specific features in development of catheter related bacteremias (CRB) in Intensive Care Units (ICU) with surgical profile at the ICU and Nephrology Clinic of the University Hospital Pleven.
Patients and methods: Fifty-two patients with clean surgical operations and central venous catheters used for total parenteral nutrition and drug admission and 52 patients with central venous catheters used for haemodialysis (control group). Microbiological study of the skin on inser-

tion site before disinfection; semiquantitative and quantitative analysis at 2 cm from the catheter tip using methods of Maki and Cleri; blood cultures obtained from the peripheral vein.

Results: Mean duration of catheterization for experimental and control groups was 10 days and 22·8 days, respectively. Skin colonization was observed in 23 cases and 36 cases, respectively. Catheter colonization was found in 32 and 26 cases, respectively. The most frequently isolated microorganisms at ICU patients were Gram negative rods – in 21 cases (65·6 per cent), followed by Coagulase negative staphylococcus – 10 cases (31·25 per cent). Coagulase negative staphylococcus – in 19 (73·07 per cent) cases, followed by S. aureus – four cases (15·8 per cent) were isolated at the control patients.

CRB were proved in 11 experimental cases (21·1 per cent) and five control group cases (9·6 per cent). Six out of all CRB in ICU were developed after catheter had been used more than seven days, four CRB – more than 14 days and one CRB – more than 21 days. CRB in the control group had been developed after catheter use more than 14 days. The most frequently observed CRB agents in ICU were Gram negative rods – nine cases (81·8 per cent), and at control group – Staphylococcus – three cases (60·0 per cent).

Conclusions: Frequency of CRB is significantly higher in surgical ICUs compared to other low risk units. CRB is earlier developed and Gram negative rods are the dominating microorganisms. Catheter hub, and not the skin, is the most probable way for CRB.

The present surgical infection: aetiology and optimization of therapy

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Aim: To study the aetiology of present surgical infection and examine their sensitivity to antibiotics. We analysed results of conventional bacteriological investigations during 1995–1997 of 478 cases, in which 424 aerobically bacteria colonized.

Results: From 424 cases were microbial colonia in monocultura 403 (95 per cent) and in association – 21 (5 per cent). Gram-negative bacteria dominated – 277 (65·3 per cent), in most cases – enterobacteria (187; 67·9 per cent). The typical association (13; 61·9 per cent) included Gram-positive microbe (Staphylococcus or Streptococcus) and enterobacteria. It calls one's attention on high percentage of saprophytes or conditionally pathogenic microbe – Staphylococcus epidermidis (44; 10·4 per cent) and Proteus (89; 20·9 per cent).

Generally, in microbial spectrum of present surgical infection during period 1995–1997 raised percentage of Gram-negative flora (χ^2=6·1; P<0·02). They have high level of antibiotic resistance with a tendency to increase every year.

Conclusions: 1. Today the aetiology of surgical infection is dominated by Gram-negative flora: E. Coli (18·8 per cent), Enterobacter (12·3 per cent), Citrobacter (12·3 per cent), Klebsiella (9·4 per cent), Pseudomonas (9·0 per cent) and Proteus (32·1 per cent). They have critically high levels of antibiotic resistance which increases every year. 2. In every third case the causes of surgical infection are new pathogenes (St. epidermidis and Proteus); they are typically seen in people who are immunosuppressed. 3. The initial antibioticotherapy should base on apriorally using medicine, which are effective against Gram-negative flora. Conventional antibiotics (penicillin, tetracycline and others) must exclude from present arsenal of surgical infection therapy. 4. In context of fast increasing of microbes' antibiotic resistance the tactics of present therapy of surgical infection should be corrected on base of multicentral bacteriological investigation results.

Successful conservative treatment of an infected thoracic aortic graft

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According to general surgical experience implanted infectious material must be removed. In cardiac surgery this especially is the case. In our situation conservative treatment resulted in definitive recovery.

A middle-aged woman was seen in our department because of chest pain. The detailed examination showed preliminary deBakey type III, dissection of the aorta with aneurysm formation in the chest. Using extracorporeal circulation a 30 mm sized Haemoshield graft was implanted into the sack of the aneurysm and its wall was wrapped loosely around the graft to achieve proper haemostasis. The first postoperative days were uneventful, but 10 days after the operation when the patient had been transferred to another hospital her temperature and leukocyte count was found to be elevated. Two weeks later the lady was admitted again with high fever and poor overall condition. CT showed liquid collar around the graft that turned out to be pus. We planned to replace the graft with a homograft aorta, and as a temporary solution a side and end hole catheter was guided into the cavity with CT control. Continuous sucking and rinsing with antiseptic solution was carried out accompanied by parenteral antibiotic treatment. In two weeks the patient's complaints and clinical symptoms discontinued, CT showed nearly complete regression. The catheter was removed and further antibiotic therapy was continued. A month later the disease was cured clinically and radiologically.

Infectious complications of decubitus ulcers

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Our experience showed that the open wound of a pressure sore is always contaminated with bacteria. Staphylococcus aureus, E. coli, Pseudomonas aeruginosa are more frequently identified with decubitus ulcers. This is most important for developing of the different infectious complications to patients with decubitus ulcers. These are such as phlegmonously inflamed pressure sore, infected subcutaneous necrosis of fatty tissue, inflamed bursa, osteomyelitis, sepsis. Sepsis resulting from these conditions can be life-threatening.

This study was based on 34 patients suffering with 66 IV-V stages decubitus ulcers from September 1994 to December 1997. Each patient had a full clinical examination, blood and urine laboratory study, bacteriological studies of the ulcer, blood and urine and X-ray studies. The results of the studies showed: (1) all of the patients had phlegmonously inflamed pressure sore, infected subcutaneous necrosis of fatty tissue or inflamed bursa; (2) osteomyelitis was diagnosed in 23 patients and (3) five patients had sepsis. The treatment of the first group consisted of applying a disinfectant dressing 2–3 times a day. Antibiotic therapy and emergency debridement was applied to 28 patients. The kind of antibiotic depends on results of the culture. If osteomyelitis was diagnosed resection of the infected bone was performed. The septic patients needed the most serious treatment. It consisted of earlier enumerated, a high concentration of antibiotics, detoxication therapy. One patient had a purulent pressure sore on the greater trochanter, V stage, coxitis and sepsis, was moved to a higher level of the hospital, where he died. All of the other patients recovered. The final step-plastic surgery of decubitus was performed after 6–8 weeks when ulcers became 'clean'.

Cytomegalovirus infections of the foregut in renal transplant recipients: diagnosis and treatment

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Aims: Cytomegalovirus (CMV) is the commonest infective agent in transplant recipients after the first postoperative month with the incidence of infection approaching 40 per cent. The incidence of gastrointestinal CMV disease is only 2 per cent, however, mortality is considerable if the infection is unrecognized and untreated.

Methods: We reviewed the notes of all patients undergoing transplantation at our institute between June 1989 and May 1997 to determine the incidence and outcome of CMV disease affecting the foregut.

Results: In this eight year period 610 patients underwent transplantation of which 595 received kidney alone and 15 received combined pancreas/

kidney grafts. Seventy-four patients (12 per cent) were treated for CMV disease of which 11 (1·8 per cent) had primary upper gastrointestinal CMV. Eight of the patients were CMV –ve preoperatively and received CMV +ve kidneys, two cases were CMV –ve to CMV –ve and one CMV +ve recipient received a CMV –ve kidney. All patients reported epigastric pain/dysphagia, 9/11 were pyrexial and 9/11 were leucopaenic. The CMV antigenaemia assay was performed on a buffy coat preparation for the detection of CMV late antigen (pp65). All patients underwent endoscopy with mucosal biopsies taken and stained with haematoxylin and eosin, diagnosis being confirmed by the identification of CMV inclusion bodies (Owl's eye appearance). All patients were treated with intravenous gancyclovir for a median of 21 days (10–21 days). Four of the patients relapsed and required further treatment with gancyclovir.

Conclusion: Upper gastrointestinal tract infection with CMV is a rare but important cause of morbidity in the post-transplant period. A suspicion of CMV in patients with fever and dysphagia, followed by rapid diagnosis and treatment has led to a dramatic improvement in the outlook for this condition.

Muscular hydatid disease: a rare infection

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Introduction: Primary muscular hydatid cysts are rarely seen even in endemic populations, corresponding to less than 1–5 per cent of the whole location. These cysts appear as a rapidly growing mass of soft tissue, sometimes with inflammatory signs and fistulization. This tumour must be differentiated from soft tissue neoplasm. MNR is the most accurate exam used to make such distinction. Ultrasonography and CT scan have less accuracy. The patients usually require several operations to eradicate the cysts.

Aim: This is a retrospective study of the hydatid disease affecting the muscle.

Patients and methods: Between January 1990 and December 1997 six patients underwent surgery for muscular hydatid cyst. We reviewed only primary muscular cyst located initially in the muscle. We have analysed age, sex, location, symptoms, diagnostic procedures, surgery, local relapse, and present status.

Results:

	Age	Sex	Location	Symptoms	Diagnostic	Surgery	Status
Case 1	53	F	Back	Mass	MNR	Curettage	Healthy
Case 2	56	F	Limb	Mass	MNR	Curettage	Healthy
Case 3	64	F	Limb	Mass	MNR	Compartment resection	Healthy
Case 4	70	M	Diaphragm	Vomica	CT	C+PC	Healthy
Case 5	46	M	Back	Mass	MNR	C+PC	Relapse
Case 6	60	M	Back	Mass	MNR	C+PC	Healthy

C: cystectomy; PC: pericystectomy.

Conclusions: In the differential diagnosis of growing mass of the back and extremities we must keep in mind the rare cases of hydatid cysts of muscular origin. This benign condition is easily diagnosed in CT scan or MNR exams. Fine needle biopsy (FNB) is not indicated in the cases of suspicion of hydatid disease because increase risk of infection and fistulization. Total removal of the cyst including the pericyst performed using the same techniques used in treating the hepatic or pulmonary affection.

Neutropenic enterocolitis in patients without leukemia

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Aim: The aim of the present study is to report two cases of nonleukemic neutropenic enterocolitis and review the literature.

Introduction: Neutropenic enterocolitis is a clinicopathological condition characterized by a septic or inflammatory intra-abdominal process in patients with haematological malignancy or who are neutropenic for a variety of other reasons. With the greater use of aggressive multiagent antineoplastic chemotherapy the condition is increasingly recognized. The aetiology, pathogenesis and optimal clinical management remain unclear.

Material and methods: This is a report of two cases of nonleukemic neutropenic enterocolitis in a patient after the administration of chemotherapy for lung carcinoma and in a patient with multiple myeloma. In addition to the report a medline search was carried out and all relevant papers were reviewed. Information sought included the patient's age, sex, underlying disease, clinical presentation, laboratory findings, the type of treatment and outcome.

Results: There were 37 patients. Age ranged from 6 months to 74 years. There were 21 men and 16 women. The underlying disease diagnoses were aplastic anemia in eight patients, solid tumour in 12, multiple myeloma in four, drug-induced agranulocytosis in four, polymyositis one, bone marrow transplantation one, human immunodeficiency virus infection three, cyclic neutropenia two, and in two patients no cause was found. Most patients presented abdominal pain, diarrhoea and fever, with 16 of them showing signs of peritoneal irritation. The treatment was surgical in 19 patients and non-surgical in 12, with no information available in six. Most patients operated were due to the suspicion of a perforated viscus. The outcome was recovery in 10 patients in the surgical group and seven in the non-surgical group, nine patients died in the surgical group, meanwhile six died in the non-surgical group.

Conclusions: With the greater use of aggressive chemotherapy is likely to be encountered more frequently. No obvious superiority of medical or surgical treatment. In patients who need surgery, neutropenia should not be a contraindication.

Laparotomy in treatment of intraabdominal abscesses

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Aim: Evaluation of repeated laparotomy in selected cases of intraabdominal abscesses.

Material and methods: During the years 1992–1997, 34 patients with large intraabdominal abscesses were treated by repeated laparotomy. The causes of intraabdominal abscesses were: complications after intraabdominal surgery (19 cases), peritonitis as an effect of digestive tract (five cases) or biliary (two cases) perforation, periappendicular abscesses (two cases), infected pancreatic cyst (three), unknown etiology (three). In all cases septic core body temperature was present, in eight patients increasing multiorgan failure symptoms were present. Abscesses were confirmed by USG in 34 cases (100 per cent), by CT scans in 14 patients (41 per cent).

Results: Repeated laparotomy was carried out 2–10 times in one patient (average four). Fourteen hospital deaths were noted (41 per cent) due to multiorgan failure. In further 10 patients (30 per cent) complications occurred. These were: jejunal and colic fistulas (eight), and mechanical ileus (two). The remainder of the patients left the hospital in good condition. Follow-up period without recurrence ranged from 3 months to 4·5 years.

Conclusions: Repeated laparotomy in cases of large intraabdominal abscesses is an effective method of treatment allowing constant control of the process and proper access in cases of complications.

Thoracic Surgery

Empyema thoracis: a continuous challenge

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Aim: Although empyema thoracis (ET) has been known since the times of Hippocrates, who first described its diagnosis and clinical course, it still persists as a serious thoracic infection, often associated with unacceptably high morbidity and mortality. The present study evaluates the management of 200 consecutive patients with ET treated in our department during the recent 10 year period.

Patients and methods: There were 136 male (68 per cent) and 64 female (32 per cent), aged 21–86 (mean: 51) years. Causes of ET were (post-surgical ETs excluded): pneumonia (63·5 per cent), tuberculosis (11·5 per cent), traumatic hemothorax (6 per cent), ruptured hydatid cyst (5·5 per cent), iatrogenic esophageal rupture (2·5 per cent), various (11 per cent). Diagnosis was based on clinical, radiological and pleural fluid culture findings.

Results: Our patients were divided into groups: group A with acute ET (*n*=97, 48·5 per cent) and group B with chronic ET (*n*=103, 51·5 per cent). Tube thoracostomy drainage (TS) was performed in all patients. Forty-four (45·3 per cent) patients of group A and 23 (22·3 per cent) of group B were successfully treated with TS alone. The rest, 133 patients, were submitted to thoracotomy (TT): lung decortication, Eloesser procedure, modified thoracoplasty, segmentectomy, lobectomy or combination of them. Mortality rates were 4·4 per cent in patients treated with TS and 8·2 per cent in those submitted to TT.

Conclusion: Complete drainage and full lung expansion by TS with suction are essential in the management of ET. If these conditions are not achieved operation should not be delayed.

Surgical treatment of bronchiectasis (early and late results)

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Eighty-six surgically treated patients with bronchectasis (49 female and 37 male) have been investigated and long-term results assessed by subsequent medical evaluation. Fifty-one cases were children and 14 adolescents, while 21 patients were adults.

In 39 patients bronchiectasis were sequels of acute bronchopathy in childhood, 25 with persistent or recurrent bronchopneumonia, eight cases of inhalated foreign bodies, 11 underwent surgical resection, with severe bleeding, two cases with surgical resection of localized bronchiectasis were considered in hypoglobulinanemic patients with persistent localized suppuration and symptoms refractory to medical treatment and one patient having had left lower lobectomy for bronchiectasis and athelectasis due to a double aortic arch.

The mapping of anatomic extension of the lesions was performed by bronchography and CT. Selection for surgery included patients having had cough productive sputum, refractory to medical therapy, recurrent episodes of pneumonitis and recurrent major haemoptysis.

Fifty-seven lobectomies (eight bilobectomy – LLL+ML and 13 – LLL with lingulectomy, 23 segmentectomies (six – basal, four – lingulectomies and two – underwent repeated surgical resection) and six pneumenectomies were performed.

Morbidity was seen in nine cases (four atelectasis, three incomplete re-expansion and two small bronchial leak). Hospital death occurred in one patient. Postoperatively, the evaluated long-term results showed 72 per cent of the patients were asymptomatic, 26 per cent improved and 2 per cent unchanged. It can be concluded that localized recurrent bronchiectasis refractory to medical treatment, before development of complications, the surgical resection is limited to lobectomy or segmentectomy and gives the most satisfactory results. At the stage of surgery, the compensatory emphysema is prevented and the ability of lung expand, will be remained.

Thoracic affection in the course of abdominal hydatid disease

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Introduction: Hydatid cyst, a form of echinococcosis, due to the development of hydatis of a tapeworm in the tissues, particularly of liver and lungs, in an endemic disease in our country. It is an extremely rare cause of hepatic tumours in the Western world but the most common cause of hepatic masses in Spain. Among the complications of hepatic hydatid cyst are infection, fistulas, rupture etc. Communication between the thorax and the abdomen is one of the less common but one of the most difficult to resolve.

Patients and methods: A retrospective review (since 1980) of hydatid abdominal disease with thoracic affection, also called 'hydatid hepatothoracic transits' was carried out based on our experience of 468 patients suffering abdominal hydatid disease treated at our institution. Only 15 patients fulfil the criteria of thoracic affection. We have evaluated the clinical findings, physiopathology of this complication, the surgical approach and complications. A distinction is made between this process and others such as a non communicating double hepatic and pulmonary cysts and pleural complications of hepatic hydatid cysts.

Results: Thoracic pain was the most frequent presenting symptom (71 per cent) together with dyspnoea (50 per cent). Other less frequent symptoms were bilioptisis in two cases (14·2 per cent), and vomiting in three cases (21·4 per cent). There were no clear cases of jaundice but one case presented with subicteria. There were also only two patients (14·2 per cent) with septic syndrome and finally, approximately 50 per cent of the cases presented with pain in the right hypochondria.

CT scan was used in most of the patients confirming thoracic affection in all the cases, but MRI is the current investigation having the same accuracy as CT scan. Thoracotomy was the preferred approach in nine cases and radical surgery, totally completed cystectomy, was accomplished in only five cases. Morbidity was 66 per cent (pleural effusions, wound infection etc.) and one patient died on the second postoperative day from respiratory distress. Average time spent in the hospital was 38 days (range seven to 62).

Comments: Morbidity rate was high, as most of the complications were early in our series, when the less radical techniques were used, radical techniques to treat the liver cyst (almost complete removal of the pericyst layer) and abdominal approach should be used in order to avoid complications. Only surgeons experienced in the treatment of both hepatic and thoracic diseases and also in the treatment of hydatid disease should obtain the best results.

Pulmonary seeding from iliac bone echinococcosis

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Background: Pulmonary seeding is an infrequent complication of abdominal echinococcosis. The liver is the most common location of hydatid cysts, other abdominal organs reached less than 20 per cent of the total. The lung is affected when the scolex is able to pass through the liver filter to the vena cava. Facing a pulmonary hydatidosis we must take into account an accompanying liver affection, which occurs in more than 80 per cent. Pulmonary seeding (growing of multiple cysts in both lungs) used to be caused by a ruptured myocardial or hepatic cyst. Seeding from a unique bone location is a rare condition not reported to date.

Aim: We present a unique case of pulmonary hydatid seeding from a bone located hydatidosis in a patient who was diagnosed two years before of right iliac bone cysts. No other location of hydatid cysts were found.

Clinical report: He was a 58 year old patient with no other pathological conditions. He was diagnosed nine years before with iliac bone hydatidosis and had undergone multiple surgical procedures to treat the disease. He complained of cough and thoracic pain two months before presentation, a chest X-ray showed multiple nodules 1 to 3 cm in both lungs. Pelvic X-ray showed an almost complete destruction of right iliac caused by the previous surgeries, but the hydatid disease was stable at this moment. CT-scan findings were multiple pulmonary masses, we did not find any abdominal or myocardial pathological condition. An open chest biopsy confirmed the suspicion of pulmonary hydatid seeding. Haemaglutination was positive for hydatid antigens (1/20480). Due to the massive lung infection surgery was discarded and Albendazole was started, the patient is asymptomatic at this moment and the number and size of the cysts is stable.

Comments: It is well known that pulmonary hydatid seeding can occur from ruptured cyst of the liver, from other abdominal organs, the heart and even from the soft tissue but it has not been reported the bone location as a primary site of lungs seeding. The bones are affected in less than 0·5 per cent of the total location of hydatid cysts which makes this complication so exceptional. Treatment should not differ from the usually recommended, in this case the massive affection of the lungs prevented any surgical procedure. We used Albendazole as the unique therapy reserving pulmonary transplantation in case of massive growing of the cysts.

Isolated lung perfusion with melphalan for the treatment of metastatic pulmonary carcinoma

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Aim: Currently, overall five-year survival for pulmonary metastases is low while systemic chemotherapy provides little benefit. Isolated left lung perfusion (ILuP) with melphalan for pulmonary metastatic adenocarcinoma in the WAG rat was studied.

Material and methods: On day 0, 35 WAG rats (±250 grams) were injected with 2·0×10E6 CC531S cells intravenously (iv). On day 7, rats underwent sham thoractomy; received 0·5 or 1 mg melphalan (MN) intravenously (iv); or left ILuP with buffered hespan (BH), MN 0·5 mg or 1·0 mg. On day 14, the number of pulmonary metastases were assessed by the method of Wexler. Tumour size was scored between 1+ (small) and 4+ (large). Statistical analysis was performed with ANOVA and Student's *t*-test.

Results: All rats survived ILuP. The number of left lung lesions decreased significantly in the ILuP-treated animals with MN compared to controls (see table). MN iv in a dose of 1 mg showed a bilateral decrease of pulmonary metastases whereas the group receiving 0·5 mg demonstrated no effect.

Group	Number of lesions in right lung	Score	Number of lesions in left lung	Score
1. Sham thoracotomy (*n*=6)	200	4+	200	4+
2. BH ILuP (*n*=5)	174±58	3+	171±65	3+
3. MN 0·5 mg iv (*n*=7)	200	4+	200	4+
4. MN 0·5 mg ILuP (*n*=5)	200	2+	28±16*	1+
5. MN 1·0 mg iv (*n*=6)	48±33	2+	27±16	2+
6. MN 1·0 mg ILuP (*n*=6)	200	3+	16±10*	1+

(200=200 nodules or more) (*:$P<0{\cdot}01$ compared to the non-treated right lung and control animals)

Conclusions: ILuP with MN is well-tolerated at a dose up to 1 mg, and decreased the number of metastatic pulmonary nodules significantly for all doses. Melphalan can be considered an effective agent for ILuP of metastatic carcinoma.

Localized benign fibrous tumours of the pleura: prognostic factors

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Localized fibrous tumours of the pleura, previously classified as localized mesotheliomas, either benign or malignant, originate from a noncommitted cell in the areolar tissue. The nature is established most often at the time of thoracotomy and subsequent histologic examination. Recurrences of even completely excised malignant lesion and sometimes also of benign lesion do occur as local relapse or blood-borne metasases. Five year survival in recurrent disease is poor. We present 10 cases of localized benign fibrous tumours submitted to surgical resection between 1987–1996. Mean follow-up was 41·5 months (23–60). In each one we detected the CD31 and Ki67 values by immunohistochemistry. CD31 is an endothelial cells antigen; its value indicates the vessel's density. Ki67 antibody is directed against a nuclear antigen only expressed in proliferating cells. Only three cases (30 per cent) stained strongly either for CD31 (>185 vessels/mm^2) and Ki67 (>40 per cent): one of them showed bilateral pulmonary metastases and died at 26 months after surgery, one patient showed bone metastases and died at four months after surgery, the other patient is alive and disease-free at one year after surgery. The other seven patients are alive and disease-free. These data seem to suggest that CD31 and Ki67 values could be considered prognostic factors in the evaluation of the localized 'benign' fibrous tumours of the pleura, but this must be confirmed in larger studies. If these data are confirmed it will be necessary to consider localized benign fibrous tumours with high Ki67 score and CD31 value in an intensive follow-up programme.

Value of thymectomy for myasthenia gravis

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Myasthenia gravis is an autoimmune disorder that affects the postsynaptic acetylcholine receptor of voluntary muscle. The aim of this study is to analyse the value of thymectomy in the treatment of myasthenia gravis in 102 patients operated on between 1981–1995.

The female to male ratio was 3·2 to 1. Their average age was 28·7 years, ranging from 11 to 63 years. After myasthenia gravis had been diagnosed, most patients 64 (62 per cent) underwent thymectomy within a year.

For the preoperative staging the modified Osserman classification was used. Stage I 4 (3·9 per cent), Stage II/a 31 (30·4 per cent), Stage II/b 49 (48·1 per cent), Stage III 18 (17·6 per cent). If there is no improvement with medical treatment within a year, we perform thymectomy even in Stage I. Complete removal of the thymus is the logical goal of surgical treatment, that is the reason why we use median sternotomy as an operative technique. Operative mortality did not occur.

Histological types of the removed thymus gland are thymic hyperplasia in one half of the cases, thymic persistency in one third of the cases, thymoma in 14 cases. The mean follow-up period was 72 months. Postoperative results were evaluated with Jaretzki classification as follows: remission 36 (35·3 per cent), asymptomatic 39 (38·2 per cent), improved 11 (10·8 per cent), unchanged 4 (3·9 per cent), worse 2 (1·9 per cent), died 10 (9·8 per cent). The mean wet weight of the removed thymus glands was 20·3 g. There was no relationship between the weight of the thymus glands and the severity of diseases and postoperative results. Randomized studies demonstrate that the results of thymectomy are better than those of medical treatment, although the role of the thymus in the pathogenesis of the disease is not completely understood.

Sarcomatoid carcinomas of the lung: an uncommon tumour

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Introduction: Sarcomatoid carcinomas (SC) of the lung, although rare in absolute sense (0·2–1 per cent), represent the most common malignancies of the airway that exhibit a composition by spindle or pleomorphic tumour cells. As such, there were many erroneous reports of true sarcomas made before the advent of adjunctive pathologic screening including immunohistological and ultrastructural analysis.
Material and methods: Since 1990, two patients (one man and one woman, 54 and 62 years old respectively), were hospitalized with the diagnosis of a lung mass. Both had a history of heavy cigarette smoking and they were presented with cough, haemoptysis, chest pain and diarrhoea in one case. Chest X-ray showed a single discrete mass, well circumscribed, one in right upper lobe and next in left lower lobe. Both patients had complete preoperative staging with CT-scans, tumour markers, and FNA cytologic studies which revealed non small cells lung cancer.
Results: Both patients were operated on Right Pneunonectomy and Left Lower Lobectomy were performed respectively with mediastinal lymph node dissection which revealed N2 disease in one case. Histology of these specimens revealed sarcomatoid carcinomas of the lung, using special immunohistological (reactivity for keratin, epithelial membrane antigen, collagen type IV) and ultrastructural analysis (presence of junctional complex between tumour cells, cytoplasmic skeins of intermediate filaments). Both patients had adjuvant radiation therapy. One patient (woman, 62) is still alive 25 months postoperatively, although the other patient (man, 54) died seven months after operation.
Conclusions: Despite their anaplastic character, most pulmonary SCs are deemed resectable using the criteria established by the American Joint Committee on Cancer. However, the overall prognosis is grim. Adjunctive irradiation and chemotherapy have been used, but, in general, these measures have had little beneficial effect. Improved recognition of such neoplasms should result in more specific and effective treatments for epithelial and mesenchymal malignancies of the airway.

Surgical treatment of pleural empyema: preferred methods today

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Aim: To analyse surgical treatment of pleural empyema and clotted haemothorax in our hospital.
Material and methods: Forty-three patients were treated during two and a half years. Fifteen patients had post-thoracotomy pleural empyema, 23 patients developed empyema due to other reasons and five patients had post-traumatic clotted haemothorax. Post-pneumonectomy pleural empyema was treated with omentoplasty plus partial thoracoplasty in eight cases and with myoplasty plus thoracoplasty in one case. Post-(bi)lobectomy empyema was managed by partial thoracoplasty alone (three patients) or by open-window thoracostomy followed by thoracoplasty (two patients) when gross wound infection was present. In one patient a foreign body causing empyema had to be removed. All patients, except those with open-window thoracostomies were managed by a single operation. Early empyemas with other aetiology and haemothoraces (10 patients) were managed by VATS debridement. VATS was used also in two patients for establishment of proper pleural drainage before definite operations were performed. Organizing stage empyemas (16 patients) underwent decortication and partial parietal pleurectomy.
Results: Three cases of mortality occurred after operating on patients with postthoracotomy pleural empyema (20 per cent), others recovered without major complications. During mean follow-up period of 14·8 months one recurrence of brochopleural fistula occurred and one patient died two months after the operation. VATS debridement was effective in nine patients (90 per cent), one patient needed thoracotomy and lower lobectomy due to lung abscess. All patients managed by decortication recovered without complications. During mean follow-up period of 17·8 months no mortality or recurrence of empyema occurred.
Conclusion: Early pleural empyemas can be effectively treated by VATS and organizational stage empyemas by decortication. Preferred treatment method for postpneumonectomy empyema is omentoplasty.

Role of subcarenal lymphadenectomy in peripheral T1-T2 lung carcinoma of upper right lobe

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According to Tsuchiya (1997) dissection of subcarenal nodes is unnecessary in peripheral non-small cell carcinoma both because of the very low involvement of these stations and the poor prognosis of these patients. In order to verify this statement we analysed our series of 70 upper right lobectomies for peripheral T1-T2 carcinoma histologically thus divided: 27 (38·6 per cent) squamous cell, 26 (37·1 per cent) adenocarcinoma, 13 (18·6 per cent) undifferentiated, three (4·3 per cent) bronchioloalveolar and one (1·4 per cent) carcinosarcoma. We also defined mediastinal nodal metastasis without lobar and/or hilar involvement as 'skip metastasis' classifying them as single and multilevel metastasis. We observed 17 mediastinal metastasis (11 single level skip metastasis and six non skip metastasis). Metastasis of the subcarenal nodes were present in four patients, 5·7 per cent of the cases (one single skip metastasis and three non skip metastasis). In two patients the histological type was undifferentiated carcinoma and in the other two spindle cell carcinoma. Of the four patients one died 11 months after surgery while the other three are still alive at 5, 10, and 12 months. As Tsuchiya (1997) we also observed a low incidence of subcarenal metastasis (4 per cent and 5·7 per cent respectively). However, in our opinion a complete mediastinal dissection is still a necessary procedure in intraoperative staging of peripheral T1 lung cancer.

Surgical treatment of mediastinal lymphangiomas (ML) in children

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For a period of 18 years (1981–1997) we operated on seven children with ML. The age of the patients ranged from one to six years (five girls and two boys). Five of them were with clinical signs of enlarging tumour mass in the neck, three had dyspnea and one was with deformity and venous congestion in the cervical region. All patients underwent complete clinical examination including conventional X-ray, sonography, angiography, bronchoscopy, bronchography and computertomography. In two children the tumour was found in the mediastinum and in five was located in the mediastinal and cervical region. The X-ray examination revealed tumour mass in the superior mediastinum, in five cases with homogeneous, in one child with inhomogenous and in one case – with hydroaeric level. The sonography and computertomography showed the exact localization, size, structure and the relation of the tumour with the adjacent organs. In two cases the tumour had caused compression and heavy dyspnea. Puncture of cervical lymphangioma and traheostomy were undertaken. All children were operated on – total extirpation of the tumour mass was performed. When the lesions were not well encapsulated the removal was a bit difficult. Two postoperative complications were observed – hylothorax and phlebectasis of superior vena cava. Morphologically the surgical specimens were composed of cavernous lymphatic spaces and the findings were consistent with cystic hygroma. The cystic structures were lined by endothelial cells and separated by a scant intervening connective tissue stroma. There was no well formed capsule.

Conclusion: ML, although histologically benign, tend to increase in size both by collection of fluid and budding of pre-existing spaces. In this manner they compress the vital mediastinal structures, may cause serious clinical problems and need surgical treatment. Total extirpation should be performed to prevent recurrence.

Role of video-assisted thoracic surgery (VATS) in the treatment of primary empyema thoracis (PET)

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Aim: A retrospective study was performed to evaluate the value of VATS technique in PET. Primary empyema was defined as intrapleural inflammatory process requiring evacuation without previous surgical or other traumatizing event in the field.

Material and methods: Thirty-one consecutive cases of PET were analysed. The phase of the empyema was categorized according to Moores. In 18/31 cases positive anamnesis with correct timing was found. In 13/31 cases ultrasonography with or without CT confirmed the stage of the PET. Thirty-one VATS were performed using the standard technique.

Results: Successful (no further surgery was needed) VATS procedure was performed in 9/10 cases in phase one PET (anamnesis under four weeks). 8/12 fibrinopurulent cases were solved with VATS alone (history up to 6/52). Only two out of the nine phase three were coped with VATS alone.

Conclusion: VATS seems to be the proper method of choice in PET in phase one and two (history less than 6/52). It is suitable for: 1. evacuation, debridement; 2. phase-staging, checking; 3. reconnaisance: fistula? VATS should be avoided in late phase (organizing) PET (history over six weeks).

DNA ploidy as a prognostic marker in completely resected non-small cell lung cancer

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Background: DNA content has been proposed as an indicator of outcome in several neoplasms and may reflect its biological behaviour. In the current study, the prognostic information provided by flow cytometric DNA analysis in patients with non-small cell lung cancer was assessed.

Methods: Flow cytometric DNA analysis was performed prospectively in 114 consecutive patients with non-small cell lung cancer submitted to surgery with curative intent. The influence of ploidy on the postoperative outcome was studied by both, a univariate and a multivariate analysis performed with Cox's proportional hazards regression model.

Results: Aneuploidy was found in 67 patients (59 per cent). Overall 36 month survival was 65 per cent for the euploid group and 30 per cent for the aneuploid group (P=0·002). If only stage I is considered, the 36-month survival rate was 72 per cent for patients with diploid tumours and 34 per cent for those with aneuploid tumours (P=0·007). Performing multivariate analysis adjusted for TNM stage and histologic type, bearers of aneuploid tumours exhibited higher risk of relapse (hazard ratio 2·65; CI 95 per cent 1·5–4·66; P=0·004) and death (hazard ratio 2·17; CI 95 per cent 1·08–4·39; P=0·032).

Conclusions: DNA ploidy is an independent prognostic factor of survival and tumour relapse in completely resected non-small cell lung cancer. The authors suggest that DNA ploidy could be a useful parameter in any future multifactorial analysis of outcome in such tumours.

Laser bronchoscopy and stenting: a four year experience

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Operative endoscopy of the airway is considered an effective procedure in most departments of thoracic surgery. Between 1993 and 1997 we performed 254 resections within the airway (244 with Nd:YAG Laser) in 200 patients. Thirty-four resections were performed with the flexible bronchoscope under local anesthesia and 220 with the rigid tube under deep sedation; 21 were performed in emergency. Twenty-three patients had postintubation tracheal strictures (33 treatments, 21 stents) and 133 (155 treatments, 41 stents) had malignant lesions (trachea 27, right main bronchus 32, left main bronchus 41, carina four, truncus intermedius 17, left upper lobe six, right upper lobe two, left lower lobe five). Tracheal, laryngeal and bronchial granulations were present in 21, two and four patients respectively. Other lesions were present in 18 patients (anastomotic stenosis after bronchial sleeve resection or lung transplantation in seven and four patients respectively) (31 treatments, 12 stents). Major complications during laser resection were bleeding (five), hypoxia (two), and arrhytmia (two). Two patients died within 24 hours after the procedure performed in emergency. The airway calibre was improved in 100 per cent of patients with benign lesions and 83 per cent of patients with malignancy. In the latter group patency of the trachea, main stem bronchi and truncus intermedius was improved better than lobar bronchi. All patients with malignancy underwent chemo-radiotherapy without respiratory distress; in the group of patients with malignant lesions survival was significantly better when a complete resection was performed. In conclusion, Laser resection is a safe and effective means of releasing airway obstructions. Complications and mortality are minimal. Completion therapy in patients with malignant tumours can be performed without respiratory distress.

Thymectomy for myasthenia gravis: prognostic factors and long term follow-up

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Thymectomy is considered a useful therapeutic option for patients with Myasthenia Gravis (MG). We reviewed our 25-year experience with this procedure with respect to long term outcome and analysis of prognostic factors. Between 1970 and 1996 we performed 218 thymectomies for MG. Fifteen patients were lost to follow-up; the remaining 203 (126 females and 77 males; mean age 36·2 years) form the object of our study. Fifty-six patients (27·6 per cent) had a thymoma. MG was graded according to the Osserman classification: 50 stage I (24·6 per cent), 79 stage IIA (39 per cent), 48 stage IIB (23·6 per cent), 20 stage III (9·9 per cent) and six stage IV (3 per cent). Mean duration of symptoms before the operation was 11·9 months (0·5–42 months). All thymectomies for thymoma were performed through a median sternotomy; 46 thymectomies for non thymomatous myasthenia were performed through a standard cervicotomy and the other 101 procedures were performed through a partial upper sternal – splitting incision; with this approach the resection could be extended to all the perithymic mediastinal fat tissue. Operative mortality was 0·99 per cent (two patients). Mean hospital stay was 6·4 days (7·9 days before 1980 and 4·8 after 1980). After a mean follow-up of 119 months (six to 324 months) 67 per cent of all patients improved their clinical status (21 per cent without medications and asymptomatic; 46 per cent with reduction of medications and clinically improved by at least one stage of the Osserman classification). Favourable prognostic factors were lower stage of myasthenia, absence of thymoma, younger age and short duration of the disease. Thymectomy was effective also in patients with ocular myasthenia gravis. Thymectomy presents minimal morbidity and is effective in the management of patients with mysthenia gravis at all stages of the disease. Patients with thymoma present a less favourable outcome.

Hernia and abdominal wall

Does the patient consider it satisfactory to undergo abdominal wall surgery under local anaesthesia and hospital admission less than 24 hours?

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Introduction: Early discharge units are becoming more and more established and so is surgery under local anaesthesia, especially for abdominal wall pathology. Therefore it is necessary to assess the results obtained by this type of unit.
Objective: The objective of the following study is to assess the degree of satisfaction of patients that have undergone hernioplasty and herniorhaphies under local anaesthesia and early discharge in our abdominal wall unit.
Methods: We have carried out a retrospective study of a descriptive kind in our series of 210 patients that have undergone hernioplasty and herniorhaphies under local anaesthesia and admission under 24 hours (53 umbilical hernias, 74 inguinal hernias, 48 crural hernias, 22 incisional hernias, and 13 epigastric hernias). Every one of these patients was operated on under local anaesthesia staying in hospital less than 12 hours (one night in hospital). We have polled these patients on the telephone (each of them monitored for 30 months). The questionnaire was drawn up on the basis of the most frequent questions made by the patients in checkups. We have evaluated pain during and after the operation (using a degree scale), the number and period of usage of painkillers after the operation, the most frequent concern on admission and discharge, the choice of this technique in case of private assistance, complications at home, the length of sick leave, incorporation to social life, need of admission or hospital consultation after discharge.
Results: One hundred and seventy-four patients (82·85 per cent) would agree to be operated on again under local anaesthesia, 157 patients (74·76 per cent) felt little or no pain during the operation, 33 patients (15·71 per cent) were in much pain and 20 patients (9·52 per cent) felt some pain. Forty-two per cent of the patients (87) needed painkillers at home for an average of four days. None of the patients had to return to hospital after discharge, although 16·6 per cent (35 patients) consulted their physician in connection with symptoms related to undergone surgery. One hundred and fifty-five patients (73·8 per cent) would recommend this type of surgery to an acquaintance. If they were to undergo surgery in a private hospital, 71·42 per cent (150 patients) would be operated on under local anaesthesia at equal price, this percentage would increase 8·3 per cent (167 patients in all) if the operations under local anaesthesia were more economical. The most frequent complication or discomfort at home was tightness in the surgical wound, 85·71 per cent (180 patients). The utmost concern on discharge was the opening of the skin suture, about 68 per cent (143 patients), and on admission the fact of being discharged within 24 hours, 33·3 per cent (70 patients), and the fear of relapse, 41·42 per cent (87 patients). The average time of incorporation to social life was 9·3 days and to work 25·3 days.
Conclusion: Discharge within 24 hours seems to be safe (no new admission), the method is well tolerated (83 per cent would undergo surgery under local anaesthesia with discharge within 24 hours again). As it can be seen the time on sick leave is long but the incorporation into social life is short.

Massive incisional hernia: surgical technique in the laparoscopic way

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Aim: We report the experience achieved in the treatment of the primary and postsurgical massive hernias the laparoscopic way.
Methods: A group of 30 patients with massive incisive and ventral hernias from different aetiology have been operated on the laparoscopic way in the years 1994–1996. The average postoperative follow-up was two years. The average number of wall defects was two each patients (1–6) and the surface to cover was 140 cm^2 mean (80–275). We used three gateways for access. The defect was treated with a PTFE Dual Mesh with these measures 19 × 15 cm and 10 × 15 cm. Some technical modifications have been produced in the evolution of treatment of the mesh fixing. The external knot and the articulated endostapler have given way to a total internal fixing with helicoidal clamped (Tacker).
Results: The average surgical time was 90 minutes, including three cholecystectomies, the release of adhesions and intestinal incarceration. There were no intraoperative complications or conversion to open. No hernia recurrences occurred. The average of postoperative hospital stay was 2·2 days.
Conclusions: The laparoscopic way avoids large incisions, drainage, seromas and postoperatory infections. It also shortens the hospital stay and shows obvious advantages to classic surgery.

Pseudotumorous reaction of giant cells: report of five cases

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Aim: To report and compare five cases of pseudotumorous reaction of giant cells and to discard polypropylene mesh as being responsible for this reaction.
Materials and methods: From 1991 to 1996 five patients with a pseudotumorous reaction of giant cells of abdominal wall underwent surgery. Three (60 per cent) were women and two (40 per cent) men, all of them have been operated previously and pseudotumorous reaction appeared in the surgical zone. The previous surgical procedures were: lipectomy in three cases, inguinal herniorraphy (Shouldice's procedure) in one case and repair of a ventral hernia reinforced with polypropylene prosthesis in the other case. All cases underwent large dissections. All patients underwent surgery to resect the lesion and different procedures were employed to repair the abdominal wall. All lesions were histologically evaluated with classic techniques and with electronic microscopy and polarized light.
Results: Histological evaluation of these pseudotumorous reactions showed a fibrotic wall with granulation tissue, dense collagen fibrosis and foreign body granuloma in all cases. Presence of collagen fibrosis and pseudotumorous reaction of giant cells with variegated cells is the reason that this reaction was wrongly called giant cell sarcoma not many years ago.
Conclusions: The histological analysis of all the cases reported did not show any difference between the four cases without mesh and the one with it. In all cases previous surgery was very traumatic with large dissection areas and we thought that this factor summed to an insufficient postoperative drainage of the zone and a possible own phenotypic fibrotic reaction of the patient are the responsibles of the pseudotumorous reaction. We conclude that polypropylene mesh is not responsible for this reaction.

Opinion of the patient vs that of surgeon on the hernia-repair with local anesthesia

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Aim: To compare the patient's vs surgeon's opinion after inguinal hernia repair under local anesthesia and mild sedation.
Materials and methods: Following institutional ethics committee approval from University Hospital of Valladolid and informed consent from patients, we have studied 278 patients (245 males and 33 females) from March 1997 to December 1997, mean age was 50·5 years (range 15–87) undergoing hernia-repair under local anesthesia with mild seda-

tion. No patient had systemic disease or received medication. The local anesthetic technique used was the infiltration of the operative site with 20 ml Mepivacain 2 per cent dissolved in 60 ml saline solution 0·9 per cent and 1 ml sodium bicarbonate 1 m, and the Major-abdomino-genital and Minor-abdomino-genital nerves blockade with 4 ml Mepivacain 2 per cent. The mild sedation was performed with Midazolam (0·01 mg/kg), alfentanyl (1–5 microgr/kg) and atropine (0·3–0·5). All patients were monitored with pulseoximetry, ECG and blood control pressure. At the end of procedure, we asked the patient to grade the pain with a Visual Analogue Scale (VAS) and to the surgeon, your valoration about the quality-state of patient during surgery (Good: 0–3, Regular: 4–6, Bad: 7–10).
Results:

	Good	Regular	Bad
Surgeon	219 (78·8%)	45 (16·1%)	14 (5·9%)
Patient	252 (90·6%)	21 (7·5%)	5 (1·8%)

$P<0{\cdot}05$ (χ^2-test).

Conclusions: We have found in our study that the patient's evaluation about the procedure is much better than the surgeon one. The reason can be due to the patient's psychological aspects, to the midazolam's amnesic effect or to certain degree of patient's emotional desinhibition during the operation because of the mild sedation. We have very good results on patient's global evaluation about the procedure, that is why we recommend this technique.

Surgical correction of troublesome and persistent postoperative hernias of the abdominal wall

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Introduction: Surgical correction of troublesome and persistent postoperative hernias of the abdominal wall continues to be a big problem due to the fact that yearly its frequency continues to increase.
Materials and methods: In the last four years in the first surgical department of the Medical University Pleven, 107 patients with troublesome and persistent postoperative hernias of the abdominal wall were operated on. The patients had had gynecological operations, operations for acute pancreatites, cholecystectomy, umbilical hernias etc. Some of the patients were operated two, three or more (up to seven) times. After undermining the hernial sac, debridement was performed after which inspection of the abdominal organs was done. Plastic surgery of the abdominal wall was then performed: correction with patients tissues – 57 patients, correction with BAPP – 27 and corrections with Mersilene – 23 patients.
Conclusions: 1. The tendency in our series was to perform all corrections with patients tissues. 2. In patients with a lot of musculo-fascial defects, the use of synthetic materials reduces the rate of postoperative complications – Mersiline, or Prolene, is recommended in these cases. 3. Antibiotic prophylactics in patients at risk of infection is mandatory.

Use of the components separation method for closure of abdominal wall defects

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Closing large defects of the abdominal wall usually requires an en-bloc-mobilization of the remaining abdominal wall. In cases where this is not possible, pedicled or free flaps are used. Artificial materials like Prolene or Marlex mesh may also be applied. In the acute situation of a burst belly, the wound over the intestine may be allowed to granulate and later be covered by a split thickness graft. Since all these methods are static, they do not allow a full reconstruction of the dynamics of the abdominal wall.

With the components separation method, the rectus muscles as well as the lateral musculature of the abdominal wall become available as local flaps. Since innervation and perfusion will not be altered, the muscular function of the abdominal wall is preserved. A stable closure of the abdominal wall can be obtained, avoiding artificial material like Prolene or Marlex mesh.

In contrast to the static methods mentioned above, the components separation technique is dynamic, which reflects in a good postoperative function of the abdominal wall as well as in a good long-term stability. A prerequisite for the full use of this technique is that the lateral abdominal wall is intact, especially the internal oblique abdominal muscle. In cases where parts of the lateral abdominal wall are not intact, this technique may be used segmentally combined with the use of artificial materials. The components separation method has proven an efficient and reliable technique for the closure of large abdominal wall defects.

A comparison of two 'tension free' inguinal hernia repair methods – laparoscopic hernioplasty vs anterior mesh technique

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'Tension free' hernioplasty is rapidly gaining worldwide acceptance. This report compares our results with laparoscopic hernia repair (LHR) vs anterior mesh technique according to Lichtenstein (AMT).

From 01.96–03.97 112 patients (comprising 135 hernias) were investigated in a randomized study; we performed 62 LHR and 73 AMT repairs. LHR group underwent transabdominal stapling of preperitoneal Prolene mesh. AMT group underwent open repair with 'tension free' Prolene mesh suturing.

The median long-term results were evaluated based on clinical examination six months (range 3–11) after the procedure. The patients were compared based on Nyhus classification, ASA risk scale and kind of repair. Postoperatively pain was scored in Prys-Roberts scale, it was significantly lower after LHR ($P<0{\cdot}001$). We had to abandon LHR because of serious contraindications to general anesthesia in three cases, the other three cases needed conversion to open repair for technical reasons. In one case we had to remove a mesh a few weeks after AMT due to infection. There were three recurrences: two in LHR group, and one in AMT group.

'Tension free' hernioplasty should be the procedure of choice in the inguinal hernia treatment. The results indicate that LHR is comparable to AMT procedure with respect to postoperative course and complications rate. LHR needs general anesthesia and is more difficult to perform but is better accepted by the patients than AMT repair.

Rives technique under local anaesthesia for difficult inguinal hernia repair: preperitoneal prosthetic placement through the groin

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Introduction: 25 per cent of the primary hernias and almost all of the recurrent ones require the use of prosthesis. Various techniques have been described for inserting the prosthesis through anterior approach, but only Rives technique repairs all of the herniary orifices of the inguinal region.
Method: We present the total repair of the músculopectineal orifice, through anterior via, using polypropylene mesh, located in preperitoneal space under local anaesthesia. After sectioning superficial planes there follows cremáster section, internal spermatic fascia and the total freeing of the spermatic cord coming out from the properitoneal space. Hernias are identified and the inguinal region is examined. Fascia transversalis is opened up, revealing Cooper ligament and femoral ring. We prepare the polypropylene mesh (6 × 11 cm) which is fixed medially on the posterior of the conjoint area. Follows the suture to the Cooper ligament, femoral fascia, internal inguinal ring, and transversus internal oblique muscles. The mesh stays posterior to the epigastric vessels and posterior wall.
Results: This technique has been carried out on 132 occasions. Mean operation time is 50 minutes; four wound infections; 92 patients followed-up more than two years without recurrences.

Conclusion: Although most of the hernias can be treated with techniques that make use of natural tissues or easier ways to insert the prosthesis, only Rives technique repairs the actual defect and the prophylaxis of the other herniary orifices of the inguinal region through anterior approach

Operative treatment of wide front abdominal wall defects combined with venter propendens

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Nine patients with wide or with several front abdominal wall defects, combined with venter propendens, were operated in our clinic for a period of three years (1995–1997) These patients being of a 'high risk' group underwent thorough preoperative investigations and preparation. Having in mind the age of the patients, the co-morbidity, the local status and the data of the respiratory and cardio-circulatory tests, the indications for an operation were strictly determined.

The operation passes through the following stages· an 'anchor' shaped incision and wide preparation of the cutaneo-subcutaneous tissues, revision of the underlying aponeurosis, herniotomy and closure of the diasthasis of mm recti abdominis, suturing the subcutaneous tissue and skin closure after applying Redon drainages for 48 hours

This type of combined operative treatment has several advantages On one hand the elimination of the venter propendens, being the main cause for the abdominal wall instability, opportunates an easy and safe abdominal plasty On the other hand the wide operative field facilitates the precise revision of the aponeurosis and its repair In all the patients there was no evidence of recurrent hernias or venter propendens during the follow-up period. Our observations give us the reason to recommend this type of operation as well tolerated by the patients

The open tension-free hernioplasty

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10–15 per cent of operations performed in departments of general surgery are for inguinal hernias. One hundred and ten years ago Bassini performed for the first time herniorraphy with acceptable result Since then there have been several modifications of the method The disadvantage of both the Bassini and the modified methods is closing the rings with tensions, which prompts the recurrences. Lichtenstein open tension-free hernioplasty was introduced to our department three years ago The aim of this report is to introduce the method and the early recovery results.

The author performed 71 open tension-free herniorraphies by Lichtenstein method between 1st July 1995 and 31st December 1997 According to this method the rings are closed, anteriorly with Dacron mesh. The method is simple and rapid, less painful than any other technique. Apart from two minor complications, our patients recovered without any problem The method helps to reduce the period of hospital treatment as well as that of sick-leave

Spighelian hernias

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Introduction: Spighelian hernias are rare and their diagnosis are difficult due to their intramural placement and the nonspecific symptoms After the introduction of ultrasound and CT scan as routine exams, its diagnosis has been simplified Semilunar line was first described by Adrian van der Spighel, and the first description of a semilunar hernia was done by Klinkosch in 1764 About 900 surgically treated Spighel hernias have been described Mean age of 50·5 years (range 40–70) and are more frequent in women 3-2. Right side is more frequent according to the largest series Although it can be congenital, most are acquired. Main symptoms are nonspecific abdominal pain, mass or intestinal obstruction Differential diagnosis might include lipoma, hematoma and abscess

Aim: To present our Department experience in the treatment of Spighel hernia.

Material and methods: From September 1995 to June 1997, 254 were operated on with the diagnosis of abdominal hernia (inguinal, crural, epigastric, umbilical, ventral and Spighel). Two hundred and eighty one herniorraphies were performed In six patients a Spieghelian hernia was diagnosed and surgically treated as shown in Table

	Age	Sex	Side	Size	Diagnosis	Technique	Evolution*	Drain	Discharge
1	73	Female	Left	15×5 cm	US-CT scan	Mesh	60	–	24 hours
2	55	Female	Right	12×3 cm	US	Suture	96	1	72 hours
3	68	Male	Right	6×3 cm	Clinical exam	Suture	57	–	48 hours
4	59	Male	Right	7×2·5 cm	US	Mesh†	2	–	24 hours
5	63	Female	Right	5×4 cm	Clinical exam	Suture	24	1	48 hours
6	69	Female	Right	8×4 cm	Clinical exam	Mesh	48	–	24 hours

*Months, †Doble Mesh

Results: In our series, 66·6 per cent were female and right side was more frequent (83·3 per cent) than left. In 50 per cent of the cases the diagnosis was made at examination; on the other hand, 50 per cent needed other explorations to reach the diagnosis. The mean size of the aponeutoric defect was 8·8 × 3·6 cm. In two patients (33·3 per cent) there was a slide of right colon and omentum respectively. Time of surgery was 38 minutes (range 30–55). No complications like hematoma, wound infection, seroma or mesh intolerance were observed Stay mean was 40 hours and it was lower in the prosthetic group (24 hours) Analgesic requirements were also lower in the prosthetic group, although no significant differences were observed.

Conclusions: Both suture and prosthetic techniques have good results with no complications and no relpase after a mean follow-up of 13 months (range 6–21) Patient recovery was excellent in all patients.

Tension-free hernioplasty under local anaesthesia for the ambulatory surgery of the inguinal hernia

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Introduction: Tension-free techniques of hernioplasty, based on the systematic use of prosthetic mesh are getting popular among many surgical groups We have analyzed our experience as non-specialized hernia surgeons, with the tension-free technique, local anaesthesia and outpatient surgery

Patients: From October 1989 until September 1996, 1162 patients suffering from groin hernia (n=1425) were operated on by our department in a public hospital Patients mean age was 54 (range 17–90) with a male/female ratio of 5/1. One hundred and thirty eight (9·6 per cent) of hernias repaired were recurrent. After June 1990, 784 operations (55 per cent) were scheduled as outpatient surgery All ambulatory patients had their hernia repaired under local anaesthesia (Mepivacain 0·5 per cent) and sedation with propofol. No contraindication for surgery was made because of age or overweight, and non-operative antibiotics were used

Method: Operative technique. The surgical technique most often used was the tension-free hernioplasty, modified from the description by Lichtenstein et al Briefly, in contrast to these authors we section all cremasteric fibres together with the external spermatic artery and vein and the genital branch of the genitofemoral nerve, at the level of the internal inguinal ring, to get a wide visualization of the posterior inguinal wall. Any indirect sac is opened, inspected and totally or partially excised, except if it has a broad base in which case is inverted A direct hernia is usually inverted. The defect on the transversalis fascia is then sutured with a few 3–0 polypropylene stitches The polypropylene mesh shaped is secured with the same material, caudally to the shelving edge of the inguinal ligament and cranially to the rectus sheath and the internal oblique muscle The slit made vertically to allow the pass of the cord is then closed.

Results: There were no remarkable intraoperative complications. During the immediate postoperative period were recorded 14 per cent complications (hematoma, urinary retention, seroma, abscess). Five patients (0·3 per cent) died with the associated pathology and emergency surgery (no outpatient surgery). Of 700 patients followed up (49 per cent), five recurrences have been detected (0·3 per cent).
Conclusions: Tension-free technique for groin hernia repair result in low complication and recurrence rates, are easily assimilated by most surgeons and performed under local anaesthesia, and facilitate patient's recovery and outpatient surgery.

Convalescence after inguinal herniorrhaphy

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Inguinal hernia repair is one of the most common operations performed in a general surgical work-load. Though the improvement in suture and prosthetic materials have reduced the incidence of recurrences, today many physicians suggest that a long convalescence period may reduce the rate of recurrence.
Objectives: 1. To know the opinion and the daily procedure of general surgeons and practitioner in relation to the necessary time-off work of these patients. 2. To know the clinical or personal factors that can modify their opinion.
Patients and methods: Between December 1996 and February 1997 a questionnaire was sent to all the general practitioners (GP) (n=2120) of nine Health Areas of Madrid, and to 262 Services of General Surgery of public and private hospitals all over the country. The questions asked were: 1. Following an uneventful primary unilateral inguineal hernia repair in a male between 18 and 65 years, how many days off work do you recommend? 2. Any of the following factors influence you in this time?: a) Type of hernia repair (unilateral/bilateral; direct/indirect). b) Use of a mesh. c) Physical activity of the patient at work (heavy/moderate/light). d) Surgical experience of the surgeon (staff/resident). e) Work conditions of the patient (self-employed or not). f) Wishes of the patient to prolong or reduce this time. 3. Do you usually take the decision to send the patient to work?
Results: A total of 434 general practitioners and 500 surgeons of 89 Services of General Surgery answered the questionnaire. The median time-off work recommended by the GP was 25 (7–68) days. In the surgical group was 27 (6–60) days (p:ns). The physical activity at work (98·5 per cent), the bilateral hernia (74 per cent) and the use of prosthesis (53 per cent) were the factors with the most influence in the group of GPs. Only the physical activity (94 per cent) and the number of hernias (62 per cent) were the factors that influenced the prolongation of the period of convalescence in more than 50 per cent of the surgeons. Only 28 per cent of the surgeons were responsible for the decision to send the patient to work. By contrast, 85 per cent of the GPs took this decision.
Conclusions: 1. GP and surgeons are influenced by factors that have not any consequence in the recurrence rate. 2. Though the theorical time-off work period is similar in both groups (25 vs 27) days, so many factors prolong unnecessarily this time. 3. An update of the implicated physicians is necessary to get a reduction of this excessive period of inactivity.

Method of repair for combined groin hernias

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The repair of large, recurrent and combined groin hernias with a femoral element during the open herniorraphy is performed mainly by McVay's, Kukujanov's and tension-free techniques. The aim was to work out a method applicable in these cases, providing a possibility for: better repair of the deep inguinal ring, physiological defence of the ring and the posterior wall, preservation of the anatomic structure of the groin area. This was achieved by the method containing the elements of Shouldice's and Kukujanov's techniques.
Material and method: The hernia sac(s) is removed. The iliopubic tract is divided from the inguinal ligament only in its medial half. The pubic pecten and ventral part of Cooper's ligament are approachable. Two (rarely three) stitches pass in the medial half of the latter. The transversalis fascia is cut and it only is repaired using Shouldice's technique. The stitches (inserted through Cooper's ligament) remained extrafascial. The relaxing incision is made through the rectus sheath. The stitches (inserted through Cooper's ligament), are placed also through the lateral part of the rectus sheath and are tied (Kukujanov's element). Without resection of the cremaster muscle, the spermatic cord is replaced on the new inguinal floor. The method cannot be performed in cases with extremely large femoral ring and Hesselbach's triangle. The method was performed in 168 patients, of them: 51 with combined, 18 with large and 17 with recurrent groin hernias. Only one recurrence.
Conclusion: The functional results are very good.

'One stop' day case groin hernia repair

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Traditionally, an outpatient appointment before hernia surgery is used to confirm the diagnosis, the indications for surgery and to discuss the surgical and anaesthetic options. We present our experience with a direct admission, same day service.

Patients were booked for 'One Stop' surgery if they appeared suitable on the basis of the GP's referral letter, occasionally supplemented by telephone enquiry. A standard explanatory letter was sent to patients and GPs prior to surgery. Follow-up was by postal questionnaire at a median of 16 months. There was a 94 per cent response rate.

Of 81 consecutive patients treated in the day case unit for groin hernia, 50 underwent 'One Stop' repair, 31 were seen in clinic before surgery, usually because of suspected medical co-morbidity, but no other patients accepted the option of a clinic appointment offered in the standard letter.

	'One Stop' (n=50)	Seen in clinic preoperatively (n=31)
Age (years)	54 (18–75)	51 (18–71)
Referral – surgery (weeks)	11	18
Wrong diagnosis	1	2
Local anaesthetic	36%	52%
Return to work (weeks)	2 (1–10)	3 (1–9)
Overall satisfaction	89%	73%

median (range)

One patient was deferred due to mild hypertension (declined LA) and three patients (4 per cent) were admitted overnight. Ninety-eight per cent of the 'One Stop Group' and 97 per cent of the conventional group would opt for the same approach if they developed a contralateral hernia.

'One Stop' day case groin hernia repair is a safe, acceptable technique, with a high level of overall patient satisfaction. In our experience minor queries during the postoperative period are common, so we now telephone patients at one week, with the option of attendance at the day unit, if they are worried.

Results of mesh-plug hernioplasty

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Aim: Evaluation of the mesh-plug method in the treatment of inguinal hernia in a prospective trial.
Material and methods: In the years 1992–1997, 187 mesh-plug hernioplasty was performed in 182 patients with inguinal and femoral hernia. Hernia type was evaluated according to Gilbert's (Rutkow) classification.

Type 2 and 3 was the most common, 55 and 68 patients respectively. In most patients spinal and local anaesthesia was performed, only 13 (7 per cent) had general anaesthesia. The operation was performed according to Lichtenstein and Rutkow procedure using polypropylene and polyester meshes.
Results: The duration of operation varied from 20–90 (mean 35) minutes. Depending on the anaesthesia applied, patients were mobilized on the same or next day. In most cases (75 per cent) analgesics were administered only during the operation day. Complications were observed in 11 patients (6 per cent), wound infection in four, inguinal hematoma in four, scrotal oedema in three. Hospitalization time was 2–6 days (mean four). Return to normal life activity was two weeks after the operation. Up to date follow-up 1 to 71 months, hernia recurrences were noticed in one (0·6 per cent) patient.
Conclusions: 1. Mesh-plug hernioplasty is simple and effective procedure of inguineal hernia repair. 2. This procedure enables short hospitalization and quick return to normal life activity.

Critical analysis of prosthetic mesh in hernia surgery

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Recurrent hernias remain one of main surgical problems. There is still persistent reluctance in the minds of many surgeons about the usage of mesh products. We aimed to report our experience about the rates of infection, rejection, and of hernial recurrence with the use of prosthetic mesh in the treatment of abdominal wall hernias. Between January 1976 and December 1996, 86 ventral and 15 inguinal recurrent hernias were treated. There were 32 men and 69 women, with an average age of 54 years (range: 17–84). Average follow-up was seven years. Of these, 61 (60·4 per cent) were originated from midline incisions. A polypropylene or a dacron mesh was used to reinforce repairs or to bridge tissue defects. We found a 5 per cent rate of seroma formation and a 2 per cent rate of infection. These complications were managed conservatively. Reherniation occurred in four patients (4 per cent). There were no complications related to adhesions, erosion of the viscera, bowel obstruction and fistula formation. This study suggests that the problem of hernia recurrence can be effectively solved by using prosthetic mesh.

Surgical treatment of hernias in Kėdainiai Central Hospital

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Hernia is one of the most frequent diseases treated in the Surgical Department of Kėdainiai Central Hospital and makes up to 13·7 per cent of all operations performed in the Department.
Aim: We wanted to analyze early follow-up results of hernias surgical treatment in the Surgical Department of Kėdainiai Central Hospital.
Material and methods: Four hundred and eight hernioplastic operations were performed during the period of 1991–1996. The inguinal hernias make up the major part – 73·2 per cent, umbilical hernias – 18 per cent, and femoral hernias – 8·8 per cent. Pediatric operations make 9·6 per cent of all hernia operations. There were 62 (15·2 per cent) of incarcerated hernias. In these cases the resection of small intestine was performed. During 1995–1996 operations on adults were performed: 1) 43 per cent hernioplasty of the posterior wall; 2) 57 per cent hernioplastic modo Kimborovski (Girrard). Lately more often the back abdominal wall is strengthened, e.g. in 1991 only for 11 per cent of patients this method was used. The method of Schumacher is used for pediatric patients. Local anaesthesia was performed for 85 per cent of patients, general anaesthesia for 15 per cent of patients. Only general anaesthesia was used for umbilical and for all recurrent postoperative hernias, and it makes 5·3 per cent of all the hernias. General anaesthesia is performed for all pediatric patients. There were observed these complications: 1) the local infection of the incision – 2 per cent; 2) pneumonia – 1 per cent; 3) 3 (0·7 per cent) patients who had incancerated hernias died.
Conclusions: 1) Lately the method of strengthening of the back abdomonal wall is used more frequently. 2) The recurrent hernias are rare.

Mesh-plug inguinal hernia repair vs Bassini procedure randomized trial

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Aim: Evaluation of the mesh-plug method in the treatment of inguinal hernia.
Material and methods: One hundred and forty patients treated for inguinal hernia were submitted to randomized and prospective trial. Hernia type was evaluated according to Gilbert's (Rutkow) classification. Two types of procedures were performed: group I – (58 patients) – the Bassini operation and group II – (82 patients) – 'mesh-plug' according to Lichtenstein and Rutkow. Statistical analysis was based on t-Student and Mann–Whitney tests. There were no significant differences between the groups in the patient's age, hernia types and the types of anaesthesia.
Results: Duration of operation in group I: 30–150 minutes (mean 66·4±26), in group II: 20–90 minutes (46±15). Statistical analysis revealed significant difference between these two groups. In 34 (58 per cent) patients of group I and in 17 (22 per cent) of group II narcotic analgetics were necessary. The difference was significant at P level $<0{\cdot}05$. Postoperative complications were observed in six (10 per cent) patients from group I and in nine (11 per cent) from group II. Duration of hospitalization in group I was 3–15 days (mean 5±2), in group II 1–11 days (mean 4±2). Patients from groups I and II returned to their normal activity after four weeks and two weeks respectively. In the follow-up 1–27 months no hernia recurrences were observed.
Conclusions: Shorter operating time, less painful postoperative course and faster recovery are the advantages of mesh-plug procedure.

Prophylaxis with ampicillin-sulbactam prevents wound infections after prosthetic inguinal hernia repair

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The value of prophylactic, single dose intravenous ampicillin-sulbactam (AS) in the prevention of wound infections in patients undergoing prosthetic inguinal hernia repair was assessed. This study appears to be the first prospective double blind controlled trial addressing this tissue.

Between September 1996–December 1997, patients (n=150) undergoing primary unilateral inguineal hernia repair without systemic disease were entered our protocol. Patients were administered AS (n=75) or placebo (n=75) intravenously prior to incision according to a predetermined code which the surgeons are unaware. Lichtenstein repair under local anesthesia was the technique adopted. Age, sex, body mass index, duration of operation was recorded. Patients were evaluated one week and one month postoperatively by the same surgeon. Any discharge was sampled and cultured. Wound infection was defined as discharge from the wound with positive culture. Upon completion of the study period the code was broken and results were assessed utilizing Student's t and χ^2 tests.

Groups were well matched for age, sex, body mass index, duration of operation and postoperative complications excluding the rate of wound infections which occurred at a rate of 0 per cent in AS opposed to 8 per cent in placebo group ($P<0{\cdot}05$). Six patients in placebo group developed wound infections (8 per cent) requiring rehospitalization in five and in two patients grafts were removed due to persistent infection.

This study documented decreased rate of wound infections when single dose AS was used during Lichtenstein inguinal hernia repairs. Proponents of mesh repairs are advised to use prophylactic single dose intravenous antibiotic coverage during their repairs. AS seemed to be an effective agent in the present study.

Free radicals in the pathomechanism of haemarthrosis

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Haemarthrosis (HA) as a cause of cartilage degradation is still a problem in traumatology. Early development of arthropathies in patients active in sports is already known. We think that repeated haemarthrosis may cause such complications. Till now most studies have investigated the morphological changes following haemarthrosis and estimated the effect of haemarthrosis but only in vitro conditions. In this in vivo trial we tried to explain the blood induced morphological changes in cartilage as well as clarifying the pathomechanism of haemarthrosis via a hypothetical model. We aimed to elaborate on the role of polymorphonuclear leukocytes and oxygen radicals following acute haemarthrosis hence trying to prove an important part of our model. Twenty four mongrel dogs were used. Artificial haemarthrosis was produced in their left hind knees by intra-articular injection of their own blood. The right hind knees served as control. The dogs were divided into three groups based on the time of haemarthrosis (1–7–30 days). Samples of the condylar cartilage were submitted for biochemical examinations to measure products of lipid peroxidation (malondialdehyde) (MDA), the reduced glutathione (GSH) and the activity of superoxide dismutase (SOD) by spectrophotometry. The changes in values were expressed in percentages where the control served as zero per cent. The 30 days samples were also examined by scanning electron microscope (SEM). There were no significant differences of biochemical parameters of one day samples. By the seventh day GSH and the activity of SOD increased by 45·3±3 per cent and 27·2±5·8 per cent respectively in the HA samples, while the MDA remained practically unchanged. In the one month samples there was no further increase in the production of endogenous scavengers but the GSH level was dropped to 17·3±8·2 per cent. The activity of SOD also decreased by 5·0±4·8 per cent as compared to the control. However, the intensity of the lipidperoxidation increased by 18·8±14·9 per cent. Morphological analysis by SEM revealed some damage of the cartilage after one month. Instead of a normal surface the cartilage showed abrasion-like injuries. These results suggest that induction of protective mechanisms such as increased production of free radical scavengers may hinder lipidperoxidation in the early phase of HA. On the contrary the balance between the defensive and aggressive processes tend to shift towards the more aggressive after one month. Therefore the first detectable morphological changes following HA seem to appear after one month or even later which correlates with the biochemical variations. Our model allowed us to prove our assumption that the free radical associated reactions play an important role in the pathomechanism of HA. All of these findings have encouraged us to further continue this investigation.

Use of low molecular weight heparin (Enoxaparin) in preventing venous thromboembolism in multiple trauma patients

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Aim: To investigate the safety and effectiveness of low molecular weight heparin (LMWH) in preventing thromboembolism in immobilized multiple trauma patients.
Material and methods: Between February 1996 and May 1997, 40 mg Enoxaparin (Clexan; Eczacıbası, Rhoune-Poulenc) was given subcutaneously once daily to the immobilized multiple trauma patients who were managed at the Intensive Care Unit of Emergency Surgery Department after their diagnoses were established. Seventy-six patients who stayed at the hospital at least seven days were included in this study and Enoxaparin administration (40 mg per day) was continued until the patients were mobilized. All trauma patients with one or more following risk factors for the development of VTE (age >45 years and enforced bed rest >3 days; previous history of venous thromboembolism; Glasgow Coma Scale <7; quadriplegia/paraplegia; spine, lower extremity or pelvic fractures; injury of a major lower extremity vein; complex wound of lower extremity) were assigned to the high-risk group. If none of the factors was present, the patient was assigned to the low-risk group. Twenty-six patients in high-risk group underwent bilateral contrast venography with nonionic contrast (Omniopaque 300 mg) to screen DVT at seventh day routinely after injury. Six patients suspected of having PE on clinical findings (tachycardia, tachypnea, chest pain) in high-risk group underwent ventilation perfusion scanning. Three of 50 patients suspected of having DVT based on clinical findings (pain, swelling, calf tenderness) in low-risk group underwent venography. There were no findings suspicious of PE in this group.
Results: None of the patients developed DVT, a ventilation perfusion scanning was assessed being as a suspected PE. Bleeding complications due to the use of Enoxaparin were not observed.
Conclusion: The use of Enoxaparin in preventing VTE in multiple trauma patients is safe, effective and necessary.

Laparoscopy in blunt abdominal trauma

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Aim: To assess the safety and efficacy of diagnostic laparoscopy in the diagnosis of intra-abdominal injuries in hemodynamically stable trauma patients, in absence of peritonitis, presence of severe concomitant injuries, objective difficulties in obtaining diagnosis, as well as to directly compare laparoscopic findings with the results of subsequent laparotomy in each patient.
Material and methods: Between January 1993 and December 1997, 51 patients with blunt abdominal trauma who were hemodynamically stable underwent diagnostic laparoscopy. All laparoscopic examinations were performed in the operating room under general anesthesia in 40 patients and local anesthesia in 11 patients. The laparoscope was introduced via a canula in the infraumbilical position. A 10–14 mmHg pneumoperitoneum is created using Verres needle, 10-mm umbilical trocar and one or two 5-mm trocars are inserted for manipulation. The mean time for performing laparoscopy was 27·1 minutes. No complications related to laparoscopy occurred.
Results: There were 36 males and 15 females ranging in age from 17 to 83 years old (mean = 35·2 years). Evidence of intraperitoneal injury was identified at laparoscopy in 41 patients. In 33 of these, laparotomy was felt to be necessary based upon the laparoscopic findings. Subsequent exploration revealed injuries requiring open treatment in all 33 patients. In eight patients injuries (six patients with hepatic bleeding I-II grade injuries) were treated, using laparoscopic technique. Ten of the laparoscopies were with no evidence for intraperitoneal injury. But in one patient a small bowel injury was missed.
Conclusions: In our patients diagnostic accuracy was 98·1 per cent, sensitivity – 88·9 per cent and specificity – 85·6 per cent. Diagnostic laparoscopy resulted in 0 per cent nontherapeutic laparotomy rate. Thus, diagnostic laparoscopy could be safely performed in the hemodynamically stable blunt abdominal trauma patients, who have indication for laparotomy based on standard diagnostic criteria. Laparoscopic findings in the most cases predicted the need of subsequent laparotomy.

Monitoring of oxidative stress parameters after resuscitation following haemorrhagic shock

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The haemorrhagic shock (HS) is a major factor contributing to fatality in polytrauma patients. Nowadays in clinics urgent intravascular volume restoration and tissue perfusion is widely accepted as an important part of management. However, reperfusion injury is a special side effect of this beneficial intervention due to escalation of oxidative stress. Because the kidney is amongst the first organs to be affected by HS, in our in vivo study we aimed to elaborate on the effects of resuscitation on kidney following such an insult. In contrast to clinical practice we were able to compare blood samples taken peripherally to that taken from the renal vein itself, paying particular attention to markers of reperfusion injury. HS was induced in 11 mongrel dogs by way of artificial bleeding, lowering the mean arterial pressure (MAP) to 45±5 Hgmm. This pressure was maintained for two hours. Then blood was reinfused over 30 to 45 minutes and the dogs were observed for a further two hours. Haemodynamic parameters, ECG and capillary flow by laser Doppler were registered continuously. Blood samples were taken at certain time points throughout different phases of the experiment. Product of lipid peroxidation (malondialdehyde) (MDA), reduced glutathione (GSH) and the activity of superoxide dismutase (SOD) were measured by spectrophotometric method. The stimulated superoxide radical generating capacity and the lag time of polymorphonuclear leukocyte (PMN) activation were also measured. Tissue samples from the kidney were taken for measurement of the same parameters. It was observed that although MAP normalized (85·1±5·5 Hgmm) by the end of reperfusion, the rate of microcirculation in kidney remained subdued by 32 per cent throughout reperfusion. We found changes in MDA to be statistically insignificant, yet scavenging activity of GSH was noticeably lower (from 21·9±0·9 to 12·7±0·7 nmol/ml) in blood taken directly from renal vein when compared to peripheral blood. Free radical production capacity of PMN's showed a gradual decline in both types of blood samples; however, discrepancies were observed in the lag time. Namely there was a gradual rise in the peripheral blood whilst in renal vein samples after an initial fall to 1·0±0·3 seconds from 1·3±0·1, a sharp increase was noticed following reperfusion (2·2±0·2 seconds). In conclusion it is evident that following resuscitation from haemorrhagic shock there is a triggering of oxidative stress processes with resultant decrease in scavenging activities and PMN activation. Secondly, it has been shown that to monitor changes in these parameters they are better demonstrated by a more selective approach to blood sampling.

Duodenal injuries

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This work presents our experiences in surgical treatment of duodenal injuries caused by blunt and penetrating abdominal trauma.

Within the period 1988–1997, 12 patients were surgically treated having abdominal trauma and duodenal injuries. Clinical picture analysis elaborated the mechanisms of injuries, diagnostic procedures, the ways of surgical care as well as postoperative complications. In the same period we had 617 patients with abdominal organ injuries.

In 10 patients the injury was caused by blunt and in two patients by penetrating abdominal trauma. In only one patient the injury of duodenum was separate and in all others was associated with the pancreas, mesocolon transversum, stomach, spleen and liver injuries. Injury diagnostic was established during the operation when bile-stained duodenal contents was found and mobilization of duodenum by Kocher manoeuvre was effected. In three patients duodenal lesions were solved by only suture of perforation. Another three duodenal lesions were solved by suture with pyloric exclusion and side to side gastrojejunostomy, and in six cases injuries were solved by covering of lesion with Roux-en-**Y** duodenojejunostomy. After the operations decompression with nasogastric tube was usually continued until bowel function returned. Five lesions were localized at the second portion, and seven of them at the third and fourth duodenum portion.

As for postoperative complications we have had four wound infections. Average hospitalization used to be 17 days.

Duodenum injuries are rare, but inspection of the whole duodenum is important during the abdominal exploration. We have had the best results with Roux-en-**Y** duodenojejunostomy.

MRI vs endoscopy in the diagnostics of knee surgery

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The number of patients requiring examination and treatment due to injury of knee joint and to degenerative alterations has been increased significantly in the past years.

The authors analyse whether in their own practice the examination through non-invasive MRI or endoscopy (arthroscopy) proved to be the most expedient as well as the most economical.

From January 1, 1996 up to December 31, 1997 there were carried out on the whole 344 arthroscopy of the knee joint. Out of this patient group 142 patients required also MR examination before operation.

They compare the two examination methods – each clinical pattern treated separately – analysing their advantages as well as disadvantages, dealing beside their diagnostical accuracy with the economical aspects.

Drawing a conclusion they state that the non-invasive MR examination is very useful in the filtering out of negative cases.

The diagnostical accuracy of the examination by arthroscopy surpasses that of MR, at the same time it gives plus information of manual examination and for the time being it is less costly than that. Moreover, it provides good assistance – if necessary – in the planning immediately before the operation and the examination can be followed without delay by the operation.

Therapeutic priorities in polytraumatized patients with cranial and abdominal lesions

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The study analyses the patients who have injuries of both the head and the abdomen.

Among 5725 patients hospitalized during 1994–1995 in the Emergency Clinic Hospital 'Prof. Dr. D. Bagdasar', 1456 were polytraumatized and 1444 hospitalized in the Intensive Care Unit. Among the 1456 politraumatisms, 206 had associated craniocerebral and abdominal lesions. The most common mechanism of injury was traffic collision (*n*=156; 75·62 per cent), falls (*n*=34; 16·3 per cent), aggressions (*n*=11, 5·33 per cent) and other causes. Males (*n*=148) were most affected. The variation of age (1–84) overlapped the age pyramid.

The computed CT scanner of the head was done in all multiple trauma cases. The diagostic peritoneal lavage (DPL) (*n*=206), CT scanning of the abdomen (*n*=62) and echography were used for the diagnostic of intra-abdominal organ injuries. Among these investigations, CT scanning of the abdomen has the biggest specificity (94·7 per cent) and accuracy (94·6 per cent). Glasgow Coma Scale (GCS), Injury Severity Score (ISS), Revised Trauma Score (RTS) and Abbreviate Injury Scale (AIS) were used to assess the trauma.

In grossly hemodynamically unstable patients, hemoperitoneum was caused by spleen rupture (*n*=17). In hemodynamically stable patients, the incidence of intra-abdominal injuries was: liver (*n*=2), pancreas (*n*=4), kidneys (*n*=6), retroperitoneal hematoma (*n*=18). Peritonitus signs (*n*=18) resulted in laparotomy that identified injuries of the intraperitoneal organs: perforation of the small bowel (*n*=6), mesentery rupture (*n*=5), perforation of colon (*n*=3), stomach (*n*=1) or other stomach injuries (*n*=2). Blunt abdominal trauma without intra-abdominal organ injuries was present at 39 patients.

The mortality multifactorial analysis shows a strong correlation between mortality and shock (66 per cent), between mortality and abdominal lesions (*n*=54 per cent), and between abdominal lesions and shock (*n*=77 per cent).

The diagnosis of multiple traumas is difficult. Those patients had an altered mental status.

The analysis of prehospital and emergency service approach to isolated moderate and severe head injuries in Turkey

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Aim: This study was designed to find out the current status of the prehospital and emergency service approach to isolated severe head injuries (ISHI) admitted to a university hospital in a major city in Turkey.

Material and methods: The emergency service records of 87 isolated head injuries (Glasgow Coma Score, GCS<13) out of 1652 trauma patients admitted to our university hospital between November 1, 1996 and October 31, 1997 were analysed.

Results: Mean GCS was nine and the mean prehospital time was 52 minutes. Thirty-six (41·4 per cent) of the 87 ISHI patients were transferred from another hospital. Twenty-one (41·2 per cent) of the 51 primary arrivals came directly via the ambulance service. All 21 of these patients had their blood pressures measured and 17 of them had IV fluids started at the scene or in the ambulance. Two of these patients had endotracheal intubation and four had cervical collar on arrival. All 87 ISHI patients had their cranial CTs done in the Emergency Service Radiology Unit within one hour. Forty-five patients (52 per cent) were disposed to the intensive care unit, 28 (32 per cent) to the operating room, 14 (16 per cent) to another hospital and two (2 per cent) died in the Emergency Service.

Conclusion: The prehospital phase of our regional neurological trauma care seems to be defective and to improve this care ambulance services must be increased and the ambulance doctors must be trained, especially for cervical immobilization and endotracheal intubation.

Abdominal traumatisms: our experience

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Aim: The evaluation of abdominal traumatisms is essential for the adoption of adequate management measures. In recent years there has been a change in the treatment protocol of such cases, due to the introduction of new diagnostic techniques that allow improved evaluation and management. The protocolization of traumatized patients presently allows a more conservative approach to treatment. We report our experience in the management of abdominal injuries over a three-year period.

Material and methods: A total of 178 traumatized patients were studied. There were 127 males (71 per cent) and 51 females (29 per cent), with a mean age of 33 years (range 5–90). A total of 46 patients (25·84 per cent) suffered abdominal lesions. The causes were evaluated, along with the diagnostic methodology employed, the type of lesion involved, management protocol and outcome.

Results: Of the 46 patients with abdominal injuries, 34 (73·91 per cent) were males. Mean age was 30 years (range 7–77). Traffic accidents were the most common cause (63·1 per cent). There were 30 closed abdominal injuries (65·21 per cent), while 31 patients presented associated extra-abdominal lesions. The affected organs were the spleen (n=38), liver (n=28) and intestine (n=9). There were multiple abdominal lesions in 11 cases. Following initial patient evaluation according to protocol, the diagnostic methods employed comprised echography, CAT and punction-lavage – the latter being performed in six cases (13·04 per cent). Conservative management was adopted in 33 per cent of the liver lesions, and in 26·4 per cent of the splenic injuries. The remaining patients were all subjected to surgery. Global mortality comprised five patients (with multiple intra- and extra-abdominal lesions).

Conclusions: The protocolization of polytraumatized patients is essential in order to standardize diagnostic and therapeutic measures – particularly in cases of closed abdominal injuries. In this way the lesions may be more precisely evaluated and adequate treatment initiated on an individual basis.

The effect of somatostatin on extrahepatic biliary obstruction in rat liver

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Aim: Extrahepatic biliary obstruction causes biliary duct epithelial cell proliferation and periportal fibrosis. If the necessary intervention is not performed at the right time, the disease may progress to biliary cirrhosis. In this experimental study, the effects of somatostatin analogue octreotide on biliary duct epithelial cell proliferation and periportal fibrosis in rats with extrahepatic biliary obstruction were investigated.

Materials and methods: Thirty female Wistar-albino rats were used. Rats were separated into three groups of 10 rats. In the first group (sham operated group) only laparotomy with common bile duct handling was applied. In the second and third groups (control group and octreotide group) laparotomy and proximal common bile duct ligation are followed by 0·5 ml of saline or 6 µg/kg octreotide subcutaneously twice daily for five days were applied respectively. On the fifth day all rats had relaparotomy and blood samples were taken for serum bilirubin, alkaline phosphatase, SGOT, SGPT measurements, and hepatectomy was performed for histopathological evaluation.

Results: Histopathologically, proliferation and fibrosis scores were significantly higher in control and octreotide groups than those of sham operated group (P<0·05), and they were significantly lower in octreotide group than those of control group (P<0·05). Although the biochemical results were significantly higher in control and octreotide groups than those of sham operated group (P<0·05), there was no significant difference between control and octreotide groups (P<0·05).

Conclusions: It is concluded that extrahepatic biliary obstruction causes severe biliary duct epithelial cell proliferation and periportal fibrosis, and although octreotide prevented these complications histopathologically, there was no improvement observed in terms of biochemical parameters.

Role of Bcl-2 in zinc inhibited apoptosis of rat liver

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Apoptosis is an active DNA fragmentation and cell deletion. It is usually regulated by certain genes expression. Bcl-2 is a well documented gene which saves the cells from committing suicide and apoptotic death. Expression of this gene expands the cellular population by suppressing apoptosis. On the contrary, expression of p53 induces apoptosis and reduce cellular population mass. We have studied the role of Bcl-2 and p53 in isolated perfused rat liver (IPRL) apoptosis model by immunohistochemical staining of rat liver.

Rat livers were perfused with modified Kreb's solution containing glucose and hydroxyethyl starch (Colloid) at 37°C and oxygenated with 95 per cent O_2 and 5 per cent CO_2. Liver specimens were collected at 0, 1, 2, 3, 5 h and freeze clamped in liquid N_2. DNA was isolated using standard phenol chloroform extraction and electrophoresed on 1·5 per cent w/v agarose gel, stained with ethidium bromide 40 µg/L (w/v) and visualized by UV light.

Although there was no evidence of positive expression of this gene in the liver samples with DNA damage after 3 h warm reperfusion at 37°C. Specimens treated with zinc sulphate 25 µM + zinc ionophore 4 µM rich solution (n=8) and proved to have no DNA fragmentation on agarose gel electrophoresis have strong positive staining of Bcl-2 antigen in its cytoplasm and was also consistently associated with negative expression of p53 gene. Furthermore, rat livers treated with antioxidants N-acetyl cysteine or calcium channel blocking agents verapamil were without evidence of Bcl-2 expression.

In summary, rat liver DNA apoptotic degradation may be inhibited by zinc sulphate after induction of Bcl-2 expression. Endonucleases inhibition by zinc may play a part in the gene expression and DNA fragmentation blockage mechanism. Further study is required for more understanding of the role of Bcl-2 in rat liver apoptotic cell injury.

The effects of laparoscopic vs open bilateral truncal vagotomy on the immune system in rats

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Pneumoperitoneum was shown to be less immunosuppressive than laparotomy wounds in the rat, however, to our knowledge, no extensive experimental study has been done to compare the immune system effects of laparoscopy with laparotomy by adding a surgical procedure. We report the preliminary results of an experimental study investigating the changes in immune system in rats undergoing laparoscopic vs open (OBTV) bilateral vagotomy. Thirty-six Wistar-albino rats were divided into three groups including, the control (n:6), LBTV (n:15) and OBTV (n:15) group. Controls underwent laparotomy with a 5 cm midline incision and were sacrificed after blood was drawn from inferior vena cava for baseline values. LBTV was effected with three mini-trocars at 6–7 mm Hg of pneumoperitoneum. OBTV was performed with a 5 cm midline incision. Both of the procedures lasted 30–35 minutes. In each group, laparotomy was performed either 24 hours (n:5), or 72 hours (n:5) after the first operation and blood for analysis was obtained by puncturing inferior vena cava. CD3, CD4, CD8, B lymphocyte, macrophage and granulocyte counts were determined from blood samples by flow-cytometric analysis. As a result, CD3, CD4, B lymphocyte, macrophage and granulocyte levels were not found to be different from the controls in both the LBTV and OBTV groups at either 24 or 72 hours (P>0·05, Kruskal-Wallis). On the other hand, CD8 levels for the LBTV group at 24 and 72 hours were higher than for controls (26·3±10·2 per cent and 36·4±13·6 per cent vs 18±3·2 per cent; P<0·05, Mann-Whitney U). CD8 levels for the OBTV group at 24 hours were also higher compared to controls (32·4±3·2 per cent vs 18±3·2 per cent; P<0·05, Mann-Whitney U) but returned to baseline at 72 hours (25·8±14·9 per cent vs 18±3·2 per cent; P>0·05, Mann–Whitney U). These results suggest that laparoscopic or open bilateral truncal vagotomy does not affect the immune system quantitatively except for the increase in CD8 levels at 24 hours with both procedures which return to baseline at 72 hours with the open procedure. Pneumoperitoneum in the laparoscopic procedure may be responsible for this finding.

Analysis of neutrophils' role on incisional wound healing

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Aim: GM-CSF has been used clinically when given systematically to increase circulating neutrophils, but wound healing effects have not been systematically studied. GM-CSF may be physiologic components of a growth factor cascade within healing wounds. The aim of this study is to determine the role of neutrophils and macrophages in the pathophysiological cascade leading to incisional wound healing. In present study, cyclophosphamide and granulocyte-macrophage colony-stimulating factor (GM-CSF) were preferred because of their contrary effects on leukocytes and a number of activities.

Materials and methods: Twenty-four Wistar albino rats were used in this study. Animals were randomized into three groups, controls receiving saline, group II receiving cyclophosphamide and group III receiving granulocyte-macrophage colony-stimulating factor (1000 ng twice per day). In anesthetized rats in all the groups, blood neutrophil counts and neutrophil functions were also determined. Seventh day of wounding, rats were killed. Fresh breaking strengths of wounded skin and hydroxyproline level of wound was determined and wound healing processes was blindly evaluated by light and electron microscopy.

Results: Neutrophil counts and phagocytosis significantly increased in group III and neutrophil counts also decreased in group II (P<0·05). Wound score in the group II was significantly less than that in the groups I and III (P<0·05). Significant differences in breaking strengths were seen between group II and group III (P<0·05). Hydroxyproline levels in surgically removed wounded skin were not also significantly changed for all three groups ($P>0{\cdot}05$).

Conclusion: The present study shows that neutropenia decreases the degree of wound healing. It is concluded that PMNs may have a role in modulating wound healing. Systematically given GM-CSF can enhance the breaking strength of surgical incision during the first week after wounding.

Clinical products and secondary cicatrization in the experimental animal

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Objective: This is an attempt to determine the cicatricial effect of bidistilled water and physiological serum on secondary cicatrization and to compare the calculation of the surface area of cutaneous wounds using a direct and also indirect method.

Materials and methods: We performed a 1×1 cm cutaneous wounds on the back of white mice after depilation. We sprayed bidistilled water or physiological serum on the wounds daily, and sketched the scab's contour on tracing paper and then transferred it to millimetered cross-section paper. On the same sketch we measured the length and width of the wound and introduced the data in a statistical program for calculation of its surface area.

Results: One week after initiating the experience, we obtained a wound closure mean favourable to the group subjected to cleansing of same with physiological serum ($P<0{\cdot}0331$). In the second week we achieved very similar wound closure means without statistical significance, regarding the clinical material used for cleansing. The surface areas found did not offer any substantial difference between the calculation of the cutaneous wound's evolution obtained directly and the one obtained by the indirect method.

Conclusions: The use of physiological serum is preferable for cleansing cutaneous wounds to that of bidistilled water, to achieve favourable cicatricial effects during the first week of the healing process.

The use of bidistilled water is recommended after the first week for its similar behaviour and lower cost.

The indirect method gives reliable results in assessing the evolution of the surface area of cutaneous wounds and also shortens the measuring process.

The effects of desmopressin on coagulation system in obstructive jaundice

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Purpose: This study was created to show the effects of desmopressin on coagulation system in obstructive jaundice.

Methods: In this experimental study we used forty Wistar Albino male izogenetic rats. We divided them into four different groups. Group 1: Sham laparotomy + Placebo (SC), Group 2: Sham laparotomy + High dose desmopressin (SC), Group 3: Bile duct ligation + Placebo (SC), Group 4: Bile duct ligation + High dose desmopressin (SC).

In all groups we determined the levels of bleeding time, protrombin time (PT), activated partial thromboplastine time (APTT), fibrinogen and factor VIII activity.

Results: We found that bleeding time, PT, APTT have increased, factor VIII and fibrinogen levels have decreased as a result of obstructive jaundice. In groups who received high dose desmopressin, significantly reduced bleeding time and APTT were found. Also factor VIII activities were significantly increased after high dose desmopressin injection. There were no significant changes at PT and fibrinogen levels in desmopressin groups.

Conclusion: Bleeding time, APTT were significantly shortened after high dose desmopressin injection. Factor VIII activity levels were also increased who received high dose desmopressin. High dose desmopressin did not induce any significant changes of PT and fibrinogen. We conclude that desmopressin can positively influence the hemostatic system in patients with obstructive jaundice. The clinical importance of this hemostatic improvement deserves further evaluation.

Detection of gastrointestinal micrometastatic cells in bone marrow by immunocytochemistry and polymerase chain reaction

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The aim of the study was to detect tumour cells of gastrointestinal carcinomas with the reverse transcriptase polymerase chain reaction and immunocytology in bone marrow.

Methods: We studied 74 patients who underwent surgery for a carcinoma of the colorectum ($n=51$) and pancreas ($n=23$). Cytological samples from peritoneal cavity lavages and bone marrow aspirates were analysed using monoclonal antibodies against tumour-associated antigens (CEA, CA 19-9 and 17-1A) and cytokeratin 18 (CK-2). For RT-PCR we used specific primers for CEA. Specificity of RT-PCR and immunocytology was assessed by examination of 11 negative controls.

Results: The tumour cells were detected by immunocytochemistry in 22 per cent of colorectal and 52 per cent of pancreatic cancer patients. The use of two antibodies (CK-2 and CA 19-9) detected 92 per cent of all positive samples, whereas CK-2 and CA 19-9 stained approximate 70 per cent of all positive samples in each case. In comparison, the RT-PCR method yielded a higher detection rate 36 per cent of colorectal and 61 per cent of pancreatic cancer patients. There was a good correlation between the detection rate and tumour stage regarding all 4 mAbs and RT-PCR: the rate was significantly lower in patients with a tumour in stage I/II in comparison to stage III/IV. The occurrence of stained cells in bone marrow correlated with classical prognostic factors (TNM classification).

Conclusion: Our results show, that PCR amplification of CEA mRNA and immunocytochemical detection of micrometastatic cells in bone marrow are a useful technique.

Establishment of an experimental model of colon cancer which replicates the regional extension pattern of human colorectal adenocarcinoma

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Aim: The aim of this study was to develop an experimental model of colon adenocarcinoma based on the orthotopic implantation of tumour cells in syngenic rats, which reproduces the regional extension pattern of human colorectal adenocarcinoma.

Material and methods: *Cell cultures:* Cell line DHD/K12-PROb. *Animals:* BD-IX rats. *Tumour implantation:* Intra-caecal injection containing 1×10^6 cells in 0·25 ml of PBS. *Design:* Six groups were established according to the moment when the animals were killed: first, second, fourth, sixth, eighth and sixteenth week after inoculation. *Measurements:* Macroscopic and histological examination, with particular emphasis on caecal lesions. Tumours were classified according to the TNM system (UICC, 1987).

Results: Group 1 (animals sacrificed on the first week after inoculation): tumours were found in 90 per cent of cases (9/10), which were classified as $T_1N_0M_0$ and $T_2N_0M_0$; Group 2 (second week): tumour in 36·4 per cent of cases (4/11), classified as $T_2N_0M_0$ and $T_3N_0M_0$; Group 3 (fourth week): tumour in 54·5 per cent of cases (6/11), classified as $T_2N_0M_0$, $T_4N_0M_0$, $T_4N_1M_0$ and $T_4N_2M_1$; Group 4 (sixth week): tumour in 70 per cent of cases (7/10) and were classified as $T_1N_0M_0$, $T_2N_0M_0$, $T_4N_1M_0$, $T_4N_2M_1$ and $T_4N_3M_1$; Group 5 (eighth week): tumour in 100 per cent of cases (10/10) and were classified as $T_1N_0M_0$, $T_3N_0M_0$, $T_4N_0M_0$, and $T_4N_2M_1$; Group 6 (sixteenth week): tumour in 90 per cent of cases (9/10) and were classified as $T_4N_2M_0$ and $T_4N_3M_1$. The 82·2 per cent of the

tumours were localized in the cecum submucosae. The metastases were observed in lung, omentum, kidney, liver, small bowel and timus. Tumour cells were observed in lymphatic vessels in 55·5 per cent of the animals with tumours and in 4·4 per cent of them were observed in blood vessels.
Conclusions: Our model offers a step by step reproduction of events described for human colorectal adenocarcinoma. It was therefore easy to predict how long it would take to achieve a degree of local extension, which is essential in the design of cancer experiments.

Monitoring of evoked potentials during ischemic damage of spinal cord: experimental evaluation in a rabbit model

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Aim: Somasensory evoked potentials (SEPs), spinal evoked potentials (Spinal-Eps), and motor evoked potentials (MEPs) were monitored in a rabbit model of spinal cord ischemia to evaluate their efficacy and to determine the correlation between evoked potentials and clinical status.
Materials and methods: Thirty New Zealand white rabbits of both sexes (2·0 to 3·7 kg) were used for this study. A modified rabbit spinal cord ischemia model of infrarenal aortic occlusion for 21 minutes was employed. After baseline SEPs, Spinal-Eps, and MEPs were obtained, evoked potentials were recorded continuously during and after clamping of the aorta (30 minutes). The animals were placed in cages for neurologic evaluation at 24 hours. Finally, the spinal cord was removed for histologic study. Main outcomes measures: according to the clinical status the animals were graded into two categories: (1) Normal, and (2) Paraplegia. Neurological outcome was correlated with evoked potentials, and histopathological findings.
Results: Fifteen animals were paraplegic. MEPs were always abolished after clamping of the aorta while Spinal-Eps and SEPs still remained. The sensory evoked potentials (SEPs and Spinal-Eps) were the least sensitive to spinal cord ischemia, and their presence had no correlation with the final clinical status (50 per cent of false negatives). This was consistent with the histopathological examination that showed damage almost entirely confined to the anterior horn, while the dorsal columns were generally well preserved. High spine MEPs evoked by twitch stimulation was the best predictor of clinical outcome (0 per cent of false negatives, 0 per cent of false positives).
Conclusions: Our findings confirm the dissociation between the motor and sensory pathways, and that the anterior horn of the spinal cord is more sensitive to ischemia than dorsal columns. Because of this, SEPs and Spinal-Eps cannot be used as safe monitors of ischemia of the spinal cord. High spine MEPs evoked by twitch stimulation is the most useful method for real-time evaluation of spinal cord ischemia, and the best predictor of neurologic outcome during reperfusion.

Different patterns of Tγδ and Tαβ cell redistribution after surgical trauma

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Aim: We observed on mice that the major surgical stress (gastrectomy) may disturb the normal cell traffic selectively with increased T cell homing in intestinal Peyer's patches and lymph nodes (GALT) and with the cell displacement from peripheral blood to lymphatic organs. Present study was performed to compare human reaction after the surgical stress to animal model.
Materials and methods: We investigated the changes in the peripheral blood WBC counts, Tγδ and Tαβ cell number in patients undergoing standard surgical procedures: gastric resection, rectal resection, cholecystectomy, strumectomy. Cells were counted on the FACSTAR cell sorter.
Results: We observed that after procedures on gastrointestinal system the lymphocyte number, especially Tγδ number decreases. Other types of operations that did not affect peritoneal cavity (strumectomy) had much lesser or opposite effect on lymphocyte cell number.
Conclusion: We would suggest that described effect is provoked by homing of lymphocytes in lymphatic organs after surgical stress similarly as we had observed in the animal model.

The use of gentamicin-containing sponges in the prevention of colonic anastomotic leakage in a rat model of peritonitis

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Intestinal anastomoses in a septic environment are considerably at risk. The aim of the present study was to evaluate whether a gentamicin-containing collagen sponge had a beneficial effect on the healing of a colonic anastomosis in a rat model of peritonitis.
Materials and methods: Peritonitis was created in fourty male Wistar rats by intraabdominal implantation of a capsule containing human stools mixed with an equal volume of peptone-yeast-glucose broth, plus 10 per cent barium sulphate. One day later, the descending colon was sectioned transversely and reanastomosed using eight interrupted sutures; randomization into four groups took place (n=10). Animals in group 1 (control group) received no additional therapy. A collagen sponge was wrapped around the anastomosis in group 2. A gentamicin-containing sponge was applicated in group 3 (2·6 mg/cm^2 gentamicin), while gentamicin was administered systemically in group 4 (12 mg/kg intramuscular). Four days later, animals were sacrified. Anastomotic strength was measured while insufflating the descending colon with air at a constant rate; the pressure at the moment of anastomotic rupture ('bursting pressure') was recorded. Results were interpreted using Student's t-test.
Results: Seven animals died of sepsis during the first 24 hours after the anastomosis: two in groups 1 and 2 each, three in group 3. In all groups, a mean weight loss of approximately 25 gram was noted; however, in group 2 (collagen-sponge without gentamicin), mean weight loss was 50 gram (P<0·05). The value of the bursting pressure (SD) was 111 (22) mm Hg in group 3 (gentamicin-sponge), in group 4 (gentamicin systemically) 90 (43) mm Hg and in group 1 (controls) 88 (49) mm Hg (P>0·05). In group 2 (collagen-sponge), bursting pressure was 7 (21) mm Hg (P<0·001 when compared to groups 1, 3 and 4): seven out of eight rats had an open perforation.
Conclusions: Local application of a collagen sponge in an infected environment severely compromises wound healing. Use of a gentamicin-containing sponge does not increase significantly the strength of an intestinal anastomosis in the rat.

Murine and human macrophages respond differently to lipopolysaccharide

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Aims: Exposure to airborne endotoxin (lipopolysaccharide, LPS) during surgery results in increased serum VEGF (vascular endothelial growth factor), the most potent angiogenic factor known, in a tumour-bearing murine model. Our aim in this study was to determine the effect of LPS exposure on VEGF production by murine and human macrophages.
Methods: Peritoneal macrophages isolated from LPS sensitive (HEN) and LPS resistant (HEJ) mice were adhered and stimulated *in vitro* with LPS (1 ng to 100 ng) for 24 hours. Human monocytes were isolated from peripheral blood, matured to macrophages *in vitro* and activated with interferon-γ. They were incubated with LPS (1–100 ng) for 24 hours. VEGF mRNA expression was determined semi-quantitatively by rt-PCR (reverse transcriptase polymerase chain reaction) and VEGF protein levels were determined by ELISA.
Results: VEGF mRNA and protein expression were not significantly altered in LPS-stimulated peritoneal macrophages isolated from LPS sensitive or LPS resistant mice. In contrast, human macrophage VEGF

mRNA expression is increased in response to LPS in a dose-dependent manner.

Conclusion: In the murine model, LPS does not directly elicit VEGF production by macrophages whereas human macrophages demonstrate increased VEGF production following LPS exposure. This finding emphasizes further fundamental differences between murine and human macrophages which are not, as yet, fully explained.

Effect of octreotide treatment on cytokine production in acute pancreatitis in rats

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Aim: To determine the effect of octreotide treatment on the cytokine production in acute necrotizing pancreatitis in rats.

Methods: Acute pancreatitis was induced by the retrograde injection of taurocholic acid into the pancreatic duct in male Wistar rats. The serum amylase activity, the wet pancreatic weight/body weight ratio, and the TNF and IL-6 levels were measured. Four µg/kg octreotide was administered subcutaneously at the time of induction of pancreatitis and 24 or 48 hours later. Rats were sacrificed 6, 24, 48, 72 hours after the operation.

Results: Serum amylase levels and pancreatic weight to body weight ratio decreased significantly ($P<0·05$) in the octreotide-treated group. Serum TNF levels decreased significantly in the octreotide-treated group as compared to the control group at 6, 24 and 48 hours (0·57±1·51 U/ml; 2·0±3·34 U/ml, 0 U/ml versus 50±15·49 U/ml; 37·5±18·37 U/ml; 13·125±12·51 U/ml, respectively).

Conclusions: Octreotide has a major influence on the cytokine production in sodium taurocholate-induced acute necrotizing pancreatitis in rats. Due to its complex effect octreotide can partially ameliorate the deleterious consequences of acute necrotizing pancreatitis. Elevated cytokine levels of the peritoneal fluid may be explained by the activation of peritoneal macrophages.

Protective role of truncal vagotomy in stress ulcer in short, medium and long term

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Introduction: Usefulness of truncal vagotomy in ulcer disease is more and more restricted because it does not seem to control the mediators of gastric acid secretion (gastrine, histamine) in long term. Nowadays, its indications seem to be limited to those complications directly related to cholinergic way (mainly those related to stress).

Aim: To assess the protective role of truncal vagotomy in short, medium and long term in animals under stress.

Materials and methods: Eighty Wistar rats were operated: truncal vagotomy, pyloroplasty and Heller's esophagic myotomy. We established four groups with 20 animals in each one, in relation to postoperative period before their sacrifice: A (long term) 120 days, B (medium term) 30 days, C (short term) 7 days and D (control, non-operated). Before they were sacrified, 10 rats in each group were under stress and we subsequently assessed gastric bleeding and erosive mucosal lesions. We also measured pre and postoperative gastrinemia levels with and without stress.

Results: Eight of 10 animals under stress in group D had gastric bleeding and erosions but only two in group C and one in groups B and A. Gastrinemia levels were worthless.

Conclusions: Our results point out that truncal vagotomy seems to protect from stress ulcer in short, medium and long term in Wistar rats.

We know about the variations of hormonal mediators of gastric acid after vagotomy in rats (double increase of G cells hyperplasia in short and long terms)[1] so we can suspect that the main mediator of stress is the acetylcholine and not gastrin. In this way, truncal vagotomy could still be in use to treat stress ulcers.

[1] Landa JI, Alcalde J, Yuste P, Ortega L, Ramia JM, Carrillo A, Balibrea JL. Influencia de la vagotomia troncular sobre las células G y D en el antro gástrico del cobaya. Cir Esp 1995; 58(3): 212–215.

An improved method for producing hepatic cirrhosis in rats

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Many models of carbon tetrachloride (CCL4) induced liver cirrhosis in the rats have been described. Nevertheless reproduction and persistence of cirrhosis is still hard to obtain.

Methods: Cirrhosis was produced in three rat series since 1988 (n=79) by a nine-week period of combined subcutaneous and gastric administration of CCL4. CCL4 was given once a week by intragastric route in doses increasing from 0·05 ml to a 0·40 ml maximum, adapted to the change in body weight. In addition, CCL4 dissolved in 50 per cent mineral oil was given once a week. A subcutaneous dose of 0·2 ml/150 g/body weight three days after the intragastric administration was given. The presence of ascitis, serum levels of albuminemia, bilirubinemia and ASAT were recorded and compared with a control group. Histological examination was made to confirm the cirrhotic state at two weeks, and at two and five months after the end of CCL4 administration. A control series (n=8) given only water was used for statistical analysis by Student's t-test.

Results: Thirty-three out of 79 rats (42 per cent) were alive at the end of the procedure. Histological evidence of micronodular cirrhosis was confirmed in 31 of 33 (94 per cent). Ascitis was 3·8±0·6 ml and 0·00 ml in control group (n=8) ($P<0·001$). ASAT was 251±107 U/l and 84±9 U/l in the control group ($P<0·01$). Albuminemia was 2·08±0·6 mg per cent and 2·84±0·4 in control group ($P<0·05$). Bilirubinemia was 1·22±0·28 mg per cent and 0·16±0·05 in control group ($P<0·001$). Twenty-four out of 31 cirrhotic rats survived for two months and 12 of those 24 survived for five months, all of them with histological evidence of cirrhosis.

Conclusion: We described and adapted a CCL4 induced cirrhosis model with 94 per cent of improvement. 77 per cent of the cirrhotic rats survived two months and 38 per cent five months with histological evidence of micronodular cirrhosis. This model is easy (18 doses), fast (nine weeks), efficient (94 per cent) and stable after five months in surviving rats.

Interleukin-1β (IL-1β) effect on polymorphonuclear neutrophil tissue-accumulation after endotoxic injury

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Introduction: Systemic Inflammatory Response Syndrome (SIRS) is mediated by the activation of multiple immunologic mediators. During SIRS there is a sequestration of leukocytes in the endothelial cells in different organs. In this study we investigate the effect of the pretreatment with IL-1β on tissue leukocyte infiltration after experimental endotoxic challenge.

Materials and methods: Seventy-two female CBA/H mice, 10–12 weeks old, were divided into three groups of 24: Group 1 = Sham (normal values); Group 2 = Endotoxic shock was induced by LPS from *Escherichia coli* serotype O55:B5 125 mg/kg intraperitoneally (i.p.); Group 3 = Pretreated with IL-1β 80 ng/mouse injected i.p. 24 hours (hr) before LPS. At 1, 2, 4 and 24 hr after LPS, the animals were killed and the liver, lungs and small intestine removed (six mice per hr and group). Tissue leukocyte accumulation in the different organs was evaluated by measurement of the products derived from leukocyte degranulation (myeloperoxidase (MPO))

by spectrophotometry. Values of MPO are expressed in U/mg of protein. Differences in mean values of MP at different times were compared using Newman-Keuls's test.
Results: *Liver:* We observed a decrease in MPO levels at 24 hr in group 3 in relation to group 2. *Lung:* There was no difference between groups. *Intestine:* MPO levels increased at 1, 2, 4 and 24 hr in group 3 in relation to group 2.
Conclusions: Pretreatment with IL-1β increases the leukocyte accumulation in small intestine after endotoxic challenge. In advanced stages after the aggression the leukocyte accumulation decreases in the liver, while the lung is not affected.

Dietary fibre. The effects on experimental colonic anastomoses

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Aim: Different dietary fibres (low fiber, LF; low fibre with pectin, LFP; low fibre with karaya, LFK; standard rat chow, SD) were used to study fecal bolus effects upon the cicatrization of colonic anastomoses in rats.
Material and methods: Fifteen rats were included in each dietary group. Anastomotic cicatrization was evaluated in terms of the complications observed, bursting pressure (BP), histology, and the quantification of hydroxyproline. To this effect, a segment of colon was removed, followed by end-to-end anastomosis. The rats were reoperated after seven days, removing the colon segment containing the anastomosis. Both segments were compared in each group, and between groups.
Results: Fecal bolus weight was significantly modified in all groups, and was greatest in the SD and LFK groups, which presented more anastomotic complications. BP (mm Hg) in the intact colon (control) was greater in the SD and LFK groups (214·2±7 and 197·3±7, respectively), significant differences being observed between the SD and LFP (174·2±7) groups. BP on reintervention (day 7) was greatest in the LFP group (193·9±7), with significant differences vs the LF and LFK groups (155·5±9 and 154·2±1, respectively). Bursting wall tension (BWT) (kdynes/cm) in the controls (day 0) was significantly lower in the LF and LFP groups (50·7±2·9 and 59·5±3·4, respectively) than in the LFK and SD groups (84·7±4·1 and 91·3±3·5, respectively). In turn, anastomotic BWT (day 7) was lower in the LF group (48·2±3·2) than in the animals given pectin (65·9±3·4), karaya (66·7±4·8) and standard diet (80·3±4·8) ($P<0{\cdot}01$). Collagen concentration in the control colon was greater in the LF diet vs the other three groups ($P<0{\cdot}07$). In the colonic anastomoses the collagen contents were significantly lower than on day 0, though no intergroup differences were observed. The histological study likewise revealed no significant differences.
Conclusions: Lower fibre diets reduce the basal pressure parameters of the colon, though without affecting subsequent gains in anastomotic resistance. In turn, the improved cicatrization observed when supplementing a low fibre diet with pectin is no longer apparent when each animal is used as its own control.

Intestinal sutures in the rat: preliminary results

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One of the most important clinical advances in suture technology was the development of synthetic absorbable sutures to replace gut sutures. The role of a suture, in fact, is to realize an approaching of two ends of a continuum solution until the wound acquires enough mechanical strength. The ideal situation would be that the material disappears once the wound is sufficiently resistant, and that the utilized suturing material has a least impact on the healing process. Authors evaluate and compare the effectiveness of five synthetic absorbable sutures to other four different absorbable synthetic sutures in intestinal anastomes in the rats, as well as their impact on the normal wound healing physiopathological process. The experimental work has been performed on three groups of six rats, sacrificed after 6, 20 and 90 days respectively. The preliminary anatomopathological results show that the least interference is given by the Glycomer* 631 and the polyglycolic acid, polyglyconate gives good results, but brings a greater fibrous reaction. At a lower level polydioxanone and polyglactin acids are found, with slightly better results for the former. The evaluation of surgical characteristics has allowed the materials to be classified into three categories: one, where features like smoothness and elasticity prevail (polyglyconate and polydioxanone); another, where knot tying and knot resistance and memory are the major characteristics (Poliglycole, Polyglactin); the last class, Glycomer* 631, was significantly stronger than the braided synthetic absorbable suture and the other synthetic monofilament over the three months of implantation and it has the best surgical characteristics because it collects the best of the monofilament and braided sutures.

Reference

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Retrospective study on 407 laparoscopic cholecystectomies converted to open surgery

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Aims: Retrospective analysis of causes of conversion to laparotomy during laparoscopic cholecystectomy and type of incision performed.
Methods: A questionnaire was mailed to all surgeons independently working in Naples and its neighbouring area with experience of >100 laparoscopic cholecystectomies. Data were collected for patients converted to open surgery from February 1990 to November 1997. Twelve thousand seven hundred and eighteen cholecystectomies were performed by 33 surgeons.
Results: Four hundred and seven (3·2 per cent) patients were converted to open laparotomy. Causes of Conversion Not Related (CNR) to laparoscopic cholecystectomy have been 27 (6·6 per cent). CNR were: diagnostic failure (n=7; 25·9 per cent); equipment failure (n=9; 33·3 per cent); complications of pneumoperitoneum (n=11; 40·8 per cent). In this group one patient died (0·3 per cent) by Veress needle vascular injury. Causes of Conversion Related to laparoscopic cholecystectomy (CRC) have been 380 (93·4 per cent), and were: adhesions (n=180; 47·6 per cent) non-dissectable Calot triangle (n=76; 20 per cent) biliary and vascular anatomical variations (n=10; 2·5 per cent) advanced acute and chronic inflammations (n=25; 6·7 per cent); common bile duct lithiasis (n=19; 5 per cent); gallbladder cancer (n=11; 2·8 per cent); complications during surgical dissection (biliary: 23, 6 per cent; vascular: 36, 9·4 per cent). Mortality was absent in this group. Laparoscopic time before laparotomy has been 30±10 minutes (range 7–150). Laparotomy has been performed by subcostal access in 314 (77·1 per cent) patients, 85 (27·1 per cent) of these were minilaparotomies. In the remaining a midline incision was preferred. Laparotomics were complicated in 38 (9·3 per cent) cases, four of whom (10·5 per cent) required subsequent laparotomy.
Conclusion: Collected experiences of causes, timing, type of incision and morbidity of laparotomic conversion during laparoscopic cholecystectomy, still represent an area of concern. Regional audit is very useful and is definitively needed specially for surgeon starting laparoscopic approach or at the beginning of their surgical experience.

Second-look endoscopy with repeated injection of thrombin with adrenaline vs fibrin glue in bleeding peptic ulcer

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A prospective randomized study was conducted to assess whether a repeated injection of fibrin glue is superior over repeated thrombin/adrenaline injection.

Thirty patients with bleeding peptic gastric or duodenal ulcer (Forrest Ia or IIa) were divided into two groups, 15 patients each. In all the patients initial injection therapy with thrombin/adrenaline was used. In Group I repeated injection with thrombin/adrenaline solution and in Group II with fibrin glue (Beriplast) was performed. In four patients (26·6 per cent) of the group I (reinjection with thrombin/adrenaline) recurrent bleeding was observed. Three patients were successfully injected again, in one patient emergency gastric resection was carried out. In the group II, the authors observed one recurrent bleeding (6·6 per cent), effectively treated with repeated endoscopic injection. The mean hospital stay of the bleeding patients in the group I was 13·2 days (5–50 days), and in the group II 7·4 days (4–12 days). No mortality and complications were observed due to the applied treatment.

Summarizing, our results suggest a possibility of benefit with the second-look elective endoscopy and repeated injection of fibrin sealant.

Diagnostic laparoscopy in suspected dissemination of intraabdominal neoplasms

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Intraabdominal dissemination of cancer into parietal peritoneum, omentum or liver surface except for very rare cases could not be diagnosed preoperatively. Some data like marked weight loss, ascites and others based only on weak, poorly documented suspicion might suggest the widespread disease. Unfortunately non-invasive methods that would allow for diagnosis of peritoneal spread are currently not available. Without preoperatively confirmed dissemination laparotomy with curative intention is in these patients usually attempted but in many cases even this results in big trauma for those patients. Postoperative period is long-lasting and complications are likely to occur. We believe, that low trauma associated with laparoscopy resulting in smooth and in most cases uneventful postoperative period justifies its use in those cases. Following this at the 2nd Department of General Surgery we performed diagnostic laparoscopy in 18 patients with suspected disseminated cancer. In eight of them dissemination was confirmed without identification of the primary tumour. In five pelvic mass originating from adnexa was discovered, in three the primary tumour was located in the gallbladder, two in pancreas, one in the stomach. In each case we were able to obtain samples for pathological examination. We observed no complications related directly to the procedure. Patients received normal oral diet in the 2–3 postoperative days and went home 4–7 days after operation. Laparoscopy with its obvious advantages of minimal invasiveness allowed us to make precise diagnosis and unnecessary laparotomy was avoided.

Emergency laparoscopy in acute abdomen

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Laparoscopy with its minimal invasiveness, ability to precisely delineate diagnosis and in many cases possibility to perform final treatment is a new, promising tool in the hands of a surgeon dealing with abdominal emergencies. Low trauma associated with this procedure, short hospitalization and ability to regain normal activity within a short period of time are obvious advantages appreciated by patients. The method itself is more demanding than in elective case with precise preoperative diagnosis and requires considerable experience. The access to some organs is difficult as well as handling of friable, inflamed tissues often covered with blood, pus or debris. Taking into account the limitations of the method we believe that it could be offered to most of patients with 'acute abdomen'. At our department we performed 102 emergency laparoscopies; 16 cases of laparoscopy for abdominal trauma are excluded as they were subject to another report. We present 86 patients with 'acute abdomen' submitted to laparoscopic procedure. Preoperative diagnosis that led to the operation were as follows: appendicitis 64, ileus 7, peritonitis 7, perforated ulcer 4, pancreatitis 4. In 82·5 per cent (66 of 80) patients requiring operative management the final treatment was performed laparoscopically, in 14 (17·5 per cent) conversion to an open procedure was necessary. In six (6·97 per cent) patients no pathology requiring surgical treatment was found. In those patients unnecessary laparotomy has been avoided. In eight (9·3 per cent) cases the diagnosis was different than preoperative but requiring surgery was undertaken during laparoscopy and patients were submitted to appropriate treatment. Four of them required conversion and laparoscopy allowed for choosing proper access for open procedure. Our experience confirms well known facts that laparoscopy in abdominal emergencies gives a chance to define precisely diagnosis, perform in most cases final treatment and to reduce the number of unnecessary laparotomies. Even though the procedure is difficult, requires trained staff and expensive equipment it should be strongly recommended.

Extraperitoneal endoscopic nephrectomy using pneumoretroperitoneum under coelioscopic control

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Aim: The extraperitoneal approach is a logical access for nephrectomy with a posterior access to the renal pedicle without interference with intraperitoneal organs. We show a right retroperitoneoscopic nephrectomy (multicystic kidney) under coelioscopic control using a direct pneumoretroperitoneum.

Material: Patient is placed in the lateral decubitus position. A Veress needle is introduced at the level of the lumbar triangle in the retroperitoneal space, that is insufflated with CO_2 (12 mmHg). Development of the pneumoretroperitoneum is watched by an optic inserted via an intraperitoneal paraombilical trocar. The retroperitoneal space created by the pneumoretroperitoneum can easily be widened by blunt dissection with a 10 mm diameter coaxial laparoscope inserted through a trocar placed in the lumbar triangle. Under intra and extraperitoneal control, three other retroperitoneal trocars are then safely introduced. The pneumoperitoneum is then exsufflated in order to allow the pneumoretroperitoneum to further enlarge. The ureter after being clipped and sectioned is pulled up to visualize the hilum of the kidney. The renal artery is first controlled by clips before ligation of the vein. The nephrectomy is completed by dissection of its upper role and anterior face. The kidney is extracted in a plastic bag.

Results: This technique was applied to six patients (right/left: 3/3) for hydronephrotic kidneys (15 to 20 cm), two multicystic and one atrophic post nephritis kidneys. The mean operative time was 200 minutes and there was no blood loss. Increase of $PaCO_2$ above 44 mmHg was recorded in one patient. There was no complication.

Conclusion: The retroperitoneoscopic nephrectomy is safely feasible. The extraperitoneal working space is large enough and the intraperitoneal control avoids blind injury to intraperitoneal organs.

Gasless laparoscopic and local anesthesia in high risk patients

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Introduction: Metabolic changes associated with pneumoperitoneum are usually of little clinical significance in healthy patients but may adversely affect the outcome in patients with underlying cardiac or respiratory disease. The gasless laparoscopic method using an electric lift introduced into abdominal cavity avoid the physiopathological problems of the pneumoperitoneum and perform a safe alternative in patients with a compromised respiratory or cardiac status.

We present abdominal explorations using local anesthesia and gasless method in patients with important pulmonary or cardiac dysfunction.

Materials and methods: We performed gasless laparoscopic surgery and local anaesthesia under direct vision in three patients (age 65, 77 and 81). All patients presented serious pulmonary dysfunction.

Results: We found one abdominal infection and observed two intestinal tumour. This method permitted to do some biopsies and tumour staging without any complications.

Conclusions: Gasless laparoscopic surgery with local anesthesia represents may provide a safer alternative method of exposure for minimally invasive surgery in patients with a compromised respiratory or cardiac disease.

Gasless laparoscopic in abdominal surgery: an early experience

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Introduction: The abdominal wall lifting or gasless method presents important advantages when compared to the traditional pneumoperitoneum method. Since all operative procedures are performed under normal pressure, the complications caused by pneumoperitoneum can be avoided and, at same time, unlimited suction and irrigation can be obtained without a reduction of exposure. In addition, simple valveless trocars and conventional surgical instrument can be used.

In this communication we summarize our first experience of using gasless laparoscopic in abdominal surgery and we present the potential advantages of this technique.

Materials and methods: We performed gasless laparoscopic surgery in 20 patients: cholecystectomy (n=11), abdominal exploration and biopsy (n=3), appendectomy (n=2) and others (n=4).

We evaluated physiological effects during anesthesia, postoperative nausea and vomiting, abdominal pain and global cost.

Results: The results obtained are similar to pneumoperitoneum method, but it has been observed a global reduction of costs, less postoperative nausea, vomiting and right shoulder pain, and no cardiovascular and metabolic disturbances. We observed one wound infection as complication and two times we had to change the surgical procedure.

Conclusions: Gasless laparoscopic surgery seems to be a reliable alternative to conventional laparoscopic and demonstrate potential advantages for selected indications.

Laparoscopic fundoplication (LF): results in the first 31 patients and influence of the learning curve

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Aims: LF has been considered a good alternative to open surgery for gastro-oesophageal reflux disease. We analyse our early experience of LF with a particular attention to the learning curve.

Materials and methods: LF was attempted in 31 patients for medically unresponsive GORD (29 patients) and giant slipping hernia (two patients). Mean age was 38 yrs (23–68), 16 patients were male (51 per cent). A 360° fundopilcation was constructed in 30 cases; a 270° posterior fundopilcation in one case. Short gastric vessels section and suture of the hiatus were not routinely performed.

Results: Mean operative time was 135 minutes but was strikingly reduced from the first (170 minutes) to the second half (100 minutes) of the patients. Seven patients (21 per cent) were converted to open surgery (both patients with giant hernia). Conversion was not observed in the last 15 patients operated for GORD. A delayed gastric wall perforation was observed near a stitch of the gastric wrap (3·2 per cent). Transient (three months) dysphagia was observed in 14 patients (45 per cent), requiring open reoperation in one case (3·2 per cent). Mortality was nil. Recurrency of symptoms is present in two (6·5 per cent) cases (mean follow-up: 17 months – range: 1–40) and appeared two and four months after surgery. Twenty-eight patients (90·3 per cent) are satisfied of the results and would repeat surgery. Both patients with recurrency were in the first half.

Conclusions: The 'learning curve' plays a great role in the first results after LF. Operating time is obviously reduced with the experience. Moreover complications or recurrency of symptoms were not observed in the second half of the patients and conversion in the last 17 cases was necessary only in two patients with giant slipping hernia. Transient dysphagia is common after LF, even in floppy procedures. Section of the short gastric vessels and posterior crural suture have no influence on it in our experience. LF has been demonstrated feasible and safe as open surgery but the analysis of the results of a single surgeon must probably exclude the first phase of experience.

Influence of laparoscopic and traditional cholecystectomy on patients respiratory efficiency

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Aim: The aim of the study was to evaluate the pulmonary function test results in patients after standard and laparoscopic operations in the first two days after surgery.
Material and methods: Seventy-six patients treated for cholecystolithiasis in the clinic between 13th June and 30th November 1995 were analysed. The patients qualified for cholecystectomy were divided into two study groups. Group I (55 patients) qualified for cholecystectomy by laparoscopic technique, group II (21 patients) operated on in a traditional way. One day before operation all the patients underwent spirometric examination by means of computer spirometer 'Pneumoscreen II Jaeger Germany'. Vital capacity (VC), exhale reserve volume (ERV), forced vital capacity (FVC) and breathing reserve (BR) was calculated and arterial blood acid-based equilibrium was determined. One and two days after cholecystectomy and the same measurements were repeated in all the patients.
Results: Spirometric results showed diminished VC, FVC and BR first day after operation of 25 per cent in the patients operated on by laparoscopic technique and of 40 per cent in the group operated on in a traditional way. The recovery of those parameters to the preoperative values was slower in patients from group II. Deficiency of breath capacities two days after surgery amounts to 13 per cent in laparoscopic and 30 per cent in traditional method group respectively. All differences in the results of spirometric study were statistically significant. There was no statistically significant changes in arterial blood acid based equilibrum.
Conclusion: The results of the study suggest that laparoscopic cholecystectomy impairs breathing sufficiency of the operated patients to a lesser extent and for a shorter time span compared to a traditional cholecystectomy.

Effectiveness of laparoscopy in case of acute lower abdominal pain in female patients

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Acute Lower Abdominal Pain (ALAP) in females usually can be a problem in everyday practice.
Aim: Aim of the study was to evaluate effectiveness of laparoscopy based diagnosis and treatment algorithm in case of ALAP on young females.
Materials and methods: The criteria for the algorithm were ALAP, sex (females), fertile age (18–45), possible laparoscopy. Targets for following steps were: 1) making the decision to perform laparoscopy by screening examinations, necessary consultations by another specialist; 2) the diagnostic laparoscopy; 3) operation (laparoscopical or open); 4) making the final diagnosis on previous findings or performing another examinations. Laparoscopical findings, laparoscopical operations, histopathological findings, rate of negative appendectomy were analysed prospectively. From September till December 1977, 43 laparscopic procedures on the research group were performed.
Results: In most cases the screening tests and specialist consultation did not prescribe true diagnosis. Laparoscopical findings were: visually inflamed appendix – 21 cases, free liquid in peritoneal cavity – 7 cases, pelvic adhesions – 5 cases, ovarian cyst in 3 cases, polycystic degeneration of the right ovarium – 2 cases, torsion of ovarian cyst with intra-abdominal haemorrhage – 1 case and no visual findings of the disease – 4 cases. Following laparoscopic procedures were performed: laparoscopic appendectomy – 20 cases, aspiration of free liquid – 7 cases, laparoscopic lesion of adhesions – 5 cases, ovarian cyst resection in 4 cases, only diagnostic procedure – 4 cases, electrodestruction of the ovarian cysts – 2 cases, open appendectomy – 1 case. Postoperative histopathological findings (n=25) were: destructive appendicitis – 18 cases, ovarian cyst – 4 cases, catharal appendicitis (negative appendectomy) – 3 cases. Negative appendectomy rate decreased from 32·7 per cent to 7 per cent.
Conclusions: Introduction of laparoscopy based diagnostically and treatment algorithm in case of ALAP on female patients can be method of choice for differential diagnostics and treatment.

The effect of endoscopic retrograde cholangiopancreatography (ERCP) to laparoscopic cholecystectomy

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Introduction: Although it has a short history, laparoscopic cholecystectomy takes the place of conventional cholecystectomy in the treatment of symptomatic cholelithiasis cases. The morbidity and mortality of this procedure were noted in many studies. According to the studies the most prominent cause of conversion to open surgery is excessive inflammation and undetermination of the anatomy. It has been stated that preoperatively performed ERCP was a minor risk factor in laparoscopic cholecystectomy. We evaluated the impact of ERCP in our 715 laparoscopic cholecystectomy cases.
Patients and methods: Between March 1992–November 1997, 715 laparoscopic cholecystectomy cases were reviewed retrospectively. Patients were grouped according to age, sex, type and the duration of symptoms, previous operations, preoperative evaluation methods and procedures. The duration of the operation, intraoperative complications, postoperative morbidities and mortalities, duration of the hospitalization time were all analysed. We have operated all ERCP performed patients 24–48 hours after that procedure. Statistical analysis was done by using Chi-square (Pearson) test.
Results: Of 715 cases, 30 (4·2 per cent) patients were performed ERCP preoperatively. Eleven of these patients (36·7 per cent) were males and 19 (63·3 per cent) patients were females. Twenty-three patients (76·7 per cent) were above 65 years old and seven (23·3 per cent) were below 65 years. Patients were operated due to chronic calculous cholecystitis in nine cases (30·0 per cent), acute calculous cholecystitis in nine cases (30·0 per cent), cholecystocholodocholithiasis in nine (30·0 per cent) and gallstone pancreatitis in three (10·0 per cent). One patient (11·1 per cent) had undergone upper abdominal operations and eight patients (88·1 per cent) lower abdominal operations previously. In the 27 patients (90·0 per cent) the operation was completed laparoscopically, whereas in three patients (10·0 per cent) the operation was converted to open surgery. The conversion rate was 10·0 per cent. Indications for conversion to open laparotomies were as follows: in two cases (66·6 per cent) due to excessive inflammation and undetermination of the anatomy; one case (33·4 per cent) suspicion of common bile duct injury. This took 60 minutes in 21 cases (70·0 per cent), and in nine cases (30·0 per cent) it was found to be above 60 minutes. The learning curve was accepted as 10 operations per surgeon. According to this 22 patients (73·3 per cent) were operated by the experienced surgeons and eight patients (26·7 per cent) by the inexperienced surgeons. Intraoperative major complications were seen in one case (3·3 per cent) and minor complications were seen in five cases (16·7 per cent). There was no complication in any case postoperatively. Postoperative hospital stay was one day in 22 (73·3 per cent), longer than one day in eight cases (26·7 per cent). Mortality rate was found to be zero.
Conclusion: There were no statistically signficance in patient age, sex, conversion to open procedure, intraoperative and postoperative complication, postoperative morbidity and mortality and duration of postoperative hospitalization. According to our results, we suggest that laparoscopic cholecystectomy can be performed confidently 24–48 hours after ERCP procedure.

Laparoscopic adjustable silicone gastric banding – first experience in Slovakia

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Aim: To report on the first two cases in whom the laparoscopic adjustable silicone gastric banding system was used. The indication was morbid obesity.

Material and methods: First two operations were done in our institution in December 1997. The patients body mass index (BMI) was 47 and 38. Details of the procedure are described

Results: Both procedures were done successfully In the first case haemorrhage from the port side was observed, this caused prolongation of the operation to more than 4 hours The second one was done in 2 hours 20 minutes Postoperative course was uneventful and patients were discharged on 7th and 5th postoperative day

Conclusion: Surgical treatment of morbid obesity is the last resort for many patients. Laparoscopic adjustable silicone gastric banding according to the literature seems to be very effective operation with very low complications and mortality rate. Our first experience is encouraging

A modified laparoscopic technique of banded vertical gastroplasty for morbid obesity

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The surgical treatment of morbid obesity has become routine clinical practice Procedures that reduce gastric capacity and dietary intake are now considered preferable to those that alter food absorption as they are associated with fewer side-effects. After a training period in an animal laboratory setting, it was decided to perform a modified banded vertical gastroplasty with vertical section by a laparoscopic approach.

Surgical technique: With the patient under general anaesthesia, the surgeon stood between the patient's legs Five cannulas were distributed in the upper abdomen First the gastrohepatic ligament is opened close to the lesser curvature of the stomach 5–6 cm below the cardias and medial to the gastric vessels Afterwards the His angle is open and a vertical partition of the stomach down 5–6 cm, by using linear articulated is performed A retrogastric tunnel joining both dissected areas was created by blunt dissection under direct vision The output of the neogastric pouch is calibrated on a nasogastric tube by sintetic band of 5 cm long.

Results: In 1997, six morbidly obese patients were treated by this laparoscopic approach All patients were women with a mean age of 28 (range 20–46) years Mean body-weight was 128 (105–146) kg. Mean operating time was 200 (150–240) min

Conclusions:

1 A laparoscopic approach has obvious advantages for morbidly obese patients

2 This modified laparoscopic procedure seems to provide the same results as open technique banded vertical gastroplasty

Laparoscopic truncal vagotomy

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This report presents the technique and results of laparoscopic bilateral truncal vagotomy with or without pyloric dilatation.

Laparoscopic truncal vagotomy was performed in seven patients with chronic duodenal ulcer resistant to medical treatment

We also routinely perform pneumatic dilatation of the pylorus to avoid problems with gastric emptying after a truncal vagotomy in patients with pyloric stenosis.

A flexible gastroscope is positioned within the pylorus and performed lysis of adhesions if it is necessary laparoscopically

The results of acid secretory tests and endoscopic control were studied.

A laparoscopic approach to truncal vagotomy was performed with a mean operation time of 65 min providing low morbidity and early recovery Semiliquid diet was given in early postoperative period (24 hours after operation) and prokinetic drugs were given routinely The patient is discharged 48–72 hours after vagotomy The ulcer healed without gastric stasis as compared with the endoscopic controls at third and sixth month postoperatively Acid secretion (BAO and PAO) was reduced by 80 per cent One of our patients has had moderate diarrhoea which resolved spontaneously

Laparoscopic truncal vagotomy is a simple safety and efficient procedure with low morbidity and early recovery for the management of chronic duodenal ulcer in a group of selected patients

Comparison of different approaches for trocar placement in laparoscopic surgery

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Aim: Different approaches of first trocar placement are currently used Even so called, 'safety-trocars' are established in laparoscopic surgery After penetration of the trocar's tip, plastic shields enclose the sharpest parts of the trocar. Although complications like small bowel perforation, injury of parenchymatous organs, or vascular injury occur in very few cases, they might become life-threatening. We investigate differences of epidemiological, economical, as well as forensic aspects in the use of 'ordinary' and 'safety' trocars, but also the performance of minilaparotomy prior to trocar placement.

Patients and methods: In two different patient groups laparoscopic surgery was performed In the first group (A) (n=1800), ordinary trocars without safety-mechanism were used In group B (n=1200), at least the first used trocar was a 'safety' trocar In the most recent group of 65 patients (group C), a minilaparotomy was performed prior to trocar placement The study design is based on a retrospective analysis

Results: The overall low incidence of trocar-induced complications (0·3 per cent [n=6] group A; 0 2 per cent [n=2] group B; 0 per cent group C). However, both trocar types hold a risk of relevant trocar injury Interestingly, the complication rate of group A and group B did not differ significantly by using the Wilcoxon χ^2-test

Conclusions: The advantages in the use of safety-trocars in our study did not appear as clearly as previously suggested. Possible reason for this result is the failing release of the safety-mechanism in extremely thick abdominal wall or severe peritoneal adhesions The higher the number of patients, the more conclusive and reliable are data concerning the real advantage of safety trocars Although the number of patients with minilaparotomy might be too small to prove statistical significance, the minilaparotomy prior to trocar placement seems to be the safest method to prevent trocar-related complications

Thoracoscopy – a sufficient tool for diagnosis and treatment of lung diseases

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Aim: The aim of the study was to evaluate the efficiency of thoracoscopy in diagnosis and treatment of lung tumours, management of pulmonary emphysema and treatment of complications after open thoracic operations

Materials and methods: The studied group consisted of 62 patients (42 males and 20 females) who were subjected to 67 thoracoscopic procedures The following operations were performed 34 diagnostic thoracoscopies, 25 cases of pneumoraphie due to spontaneous pneumothorax, 10 cases of lung tumours excision, three cases of closing bronchial stump fistulas

Results: In 31 out of 34 patients (91 2 per cent) thoracoscopy allowed the histological diagnosis of lung lesion to be obtained and appropriate treatment to be introduced In 15 cases one thoracoscopic procedure and in three cases two such procedures were efficient to treat pneumothorax due to pulmonary emphysema (18 out of 25 = 72 per cent) In nine out of 10 cases thoracoscopy was efficient in radical removing of benign lung tumour Using thoracoscopy we managed to close the main bronchial stump fistula after pulmonectomy in two out of three cases There were no intraoperative or postoperative complications connected with these procedures

Conclusions: We consider thoracoscopic technique to be a suitable method for the diagnosis and treatment of pulmonary lesions

Aberrant left hepatic artery in laparoscopic fundoplication

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An aberrant left hepatic artery (AHA) arises from the left gastric artery in 10–30 per cent based on angiographic series or cadaver studies. It may concern an accessory or a solitary branch to the left liver lobe. The location of this AHA is such that it can compromise proper dissection of the hiatus in laparoscopic gastro-oesophageal reflux surgery.

Material and methods: A series of 68 laparoscopic fundoplications is studied in a retrospective manner concerning the presence and management of an AHA. Literature is reviewed.

Results: In 14 of 68 laparoscopic fundoplications (20·6 per cent) an AHA was present and complicated the procedure. It necessitated conversion in two patients, due to impaired vision on the hiatus, and was ligated in another patient which results in a transient rise of liver function tests postoperatively. Due to two dimensional vision in laparoscopic procedures and relatively fixed angle of vision, the AHA, if present, is more impairing proper hiatal dissection than in open procedures. In open esophageal or gastric surgery the occurrence of an AHA is described in approximately 20 per cent of patients and its ligation has led from a transient rise in liver function tests postoperatively to ischemia of the left liver lobe, necessitating partial hepatectomy, and even some deaths.

Conclusions: When performing laparoscopic fundoplication we must be aware of the possible presence of an AHA and, when encountered, effort should be made to preserve it, since injury can give rise to serious morbidity. Lowering of the liver retractor can reduce tension on the aberrant artery and create a greater window for hiatal dissection as well as looping the artery for careful manipulation. If proper dissection can not be insured, conversion is preferable over ligation.

Endoscopic sphinterotomy as an alternative of the operation in patients with high operative risk

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Dynamic progress of the endoscopic technique allows to remove gallstones from the main bile duct. The purpose of the study is comparison of the patients who were surgically treated on choledochal stones and through endoscopic sphincterotomy.

Between 1989–1995, 236 patients were operated on for choledochal stones. Seventy-one per cent were over the age of 65 years. Diabetes, circular insufficiency, cardiac diseases and obesity were the most common among them. In this group of patients the operative mortality accounted for nine per cent.

At the same period 612 endoscopic sphincterotomies were performed, in 321 cases – for reason of the bile duct stones. There was 56 per cent of patients over 65 years. Complications were evaluated – bleeding, acute pancreatitis and restenosis of Vater's papilla. The rate of mortality was 0·16 per cent. The cost of these two kinds of the treatment was compared. The endoscopic sphincterotomy one was over 10 times cheaper.

Conclusions: The authors believe that endoscopic sphincterotomy ought to be the main treatment of bile duct stones, particularly in patients with high operative risk.

The efficacy of laparoscopic surgery in thoracic and abdominal emergencies – preliminary report

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The endoscopic surgical procedures extended to and began to dominate more and more surgical fields. Our paper desires to show as a preliminary report the experience of an Emergency Hospital in using laparoscopy and thoracoscopy in the large area of acute surgical diseases.

Material and methods: We propose a retrospective study dealing with 369 laparoscopic and thoracoscopic procedures performed between 1 January 1995 and 31 December 1997. All of them were acute conditions. We split the heterogeneous group in two main sections: traumatic and non-traumatic including 32, respectively 333 cases with the initial specification that all items concerning 250 cholecystectomies will be subject for other papers. The purposes of performing them in these mentioned circumstances were both diagnostic and therapeutic. The 32 abdominal injuries included 10 penetrating wounds and 22 blunt traumas all of the latter concerning polytraumatized patients considered not fit for CT. The other 333 were 250 acute cholecystites, 32 perforated peptic ulcer (PPU), 27 acute pelvic diseases, 9 acute appendicitis, 4 bowel occlusions, 4 acute peritonitis, 4 acute pancreatitis, 2 reoperations, 1 foreign abdominal body. The remaining 4 observations concern 4 thoracoscopic approaches, 2 for traumatic and 2 non-traumatic conditions.

Results: All endoscopic surgery procedures were successfully performed, meaning there was no missed injury. In the trauma patient group were: 24 pure (limited to inspection and drainage or followed by laparotomy) diagnostic and 8 therapeutic laparoscopies, with 2 conversions for the penetrating injuries (1 transgastric and 1 diaphragmatic wound), respectively 5 conversions for the blunt injuries (2 for ruptured spleen, 1 for ruptured liver, 1 for ruptured small bowel and 1 for ruptured diaphragm). The therapeutic laparoscopies included 3 phrenorraphies, 2 haepatorraphies, 2 liver cautery haemostasis. There was no postoperative morbidity and only one patient died because of severe brain injury. In the 83 non-traumatic patients (excluding cholecystitis) we performed 2 pure diagnostic laparoscopies (1 bowel infarction and 1 tuberculous peritonitis) and 78 therapeutic ones with 3 conversions (1 for massive uncontrolled haemoperitoneum in ectopic pregnancy, 1 for liver and peritoneal abscesses and 1 for acute extensive necrotizing pancreatitis). There was no mortality; morbidity consisted in 1 residual abscess and 2 ileus after laparoscopic suture of PPU.

Conclusions: Laparoscopy and thoracoscopy are very useful and safe when performed in selected cases of acute abdominal and thoracic diseases. In most instances it can be carried out on therapeutic definitive purposes without conversions, morbidity and mortality. The use in trauma patients is still limited, but efficacy consists both in possible accurate diagnosis and avoidance of unnecessary extended explorative laparotomy.

Right iliac fossa pain, post appendicectomy: the role of diagnostic and therapeutic laparoscopic adhesiolysis

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Aim: To assess the role of diagnostic laparoscopy and therapeutic adhesiolysis in the management of right iliac fossa (RIF) pain, post appendicectomy.

Materials and methods: Eleven patients (9 females, 2 males, age range 18–45) presented over a 12 month period, with unremitting RIF pain. Each had previously undergone conventional open appendicectomy, for appendicitis, over a period of three months to 10 years. There was no clinical or radiological evidence of acute obstruction in any patient. All were managed conservatively initially. Abdominal and pelvic ultrasound were performed on all patients and contrast studies of the small and large bowel, where appropriate. Symptomatic relapse resulted in diagnostic laparoscopy and laparoscopic adhesiolysis being successfully performed on each patient.

Results: At laparoscopy no alternative cause for pain was identified, barring postoperative adhesions. Mean operative time for each procedure was 44 minutes. Postoperatively, analgesic requirements and symptoms were markedly reduced on visual analogue scales. Mean discharge time was 48 hours. There was no associated morbidity and no reattendance (follow up 7 months).

Conclusions: The concept of diagnostic laparoscopy and therapeutic adhesiolysis is attractive and offers all the advantages of minimally invasive surgery. Its role has been documented in the management of chronic pelvic pain and small bowel obstruction, however, it has not been formally documented in the management of post appendicectomy pain, secondary to intra abdominal adhesions. The success encountered in this short series, suggests that this is the tool of choice for the management of this condition.

Major postoperative complications and conversion causes in laparoscopic cholecystectomy for acute cholecystitis

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Introduction: The aim of our retrospective study is to analyse the causes for conversions and major postoperative complications that appeared in laparoscopic cholecystectomy (LC) for acute cholecystitis (AC) and their influence on the length of stay.

Methods and materials: We have analysed only the cases for which beside the physical examination, laboratory tests and macroscopic aspect, the diagnosis of AC was confirmed by a pathology examination.

Results: Between December 1993–November 1997, we performed 192 LC for AC. Out of these patients 50 were men and 142 women; the mean age was 53·6 years (28–81). Severe forms of AC were: gallbladder empyema 40 patients, gangrene 39 patients, strong fibrous inflammatory adhesions (SFIA) around the cholecyst 22 patients. Of all the patients, 126 were operated on within the first 24 hours from admission (65·6 per cent). Conversion was necessary for 13 patients (6·7 per cent): 9 conversions for security reasons due to unclear anatomy (eight patients with AC and SFIA) and for one patient due to cystic artery lesion; 4 necessity conversions due to the presence of stones in the common bile duct. Fourteen patients (7·02 per cent) developed 20 major postoperative complications (10·41 per cent); in this group one patient died. The complications were: infectious 5 (wound infection), haemorrhagic 3, biliary 5 (postoperative fistula 1, bile leak 1, biliary subhepatic collection 3), incisional hernia 1, duodenal fistula 1, acute pancreatitis 1, cardiopulmonary complications 4. Four patients were operated on again: three by laparotomy and one by laparoscopy. Six patients had an AC with SFIA. Mean hospital stay for LC without major complications was of 3·6 days (3–6 days). For the patients for which conversion was performed, the mean hospital stay was of 8·9 days (5–20 days) and for those with major postoperative complications 13 days (3–33 days). For those patients with AC and SFIA, the mean hospital stay was of 7·1 days (5–10 days) if conversion was performed and of 14·5 days (3–30 days) if they had major complications.

Conclusions: The rate of postoperative complications for LC for AC is acceptable compared with existing data in the literature. Once the surgeon accumulates experience, these results can be improved. In the extremely difficult cases with unclear anatomy and especially for AC with SFIA, early conversion is beneficial for the patient and the surgeon, depending on her/his experience.

Our experiences obtained in the course of performing laparoscopic cholecystectomy (LC) in acute cholecystitis

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Our Department has been accomplishing laparoscopic cholecystectomy since April 1992. One thousand three hundred patients have been treated for cholecystolithiasis till the 31st of December 1997. 93 per cent of the patients were submitted to laparoscopic cholecystectomy and 7 per cent of the patients were operated in the 'open' way. The operative mortality was 0·7 per cent among patients submitted to LC and 0 per cent among those who were operated in the traditional way.

According to the general belief the acute cholecystitis is considered even today to be a relative contraindication of LC. In the period mentioned above there were 104 patients (8 per cent) in our department who were submitted to LC owing to acute cholecystitis. Signs of inflammation without previous clinical symptoms were found in 40 per cent of elective operations. In case of acute cholecystitis proved preoperatively operative interventions were preceded by a 2–4 day long antibiotic treatment, however in subacute inflammation opus had to be postponed.

In summary, our aim is to compare our results gained during applying LC with the results of the previous 'traditional' method of operations in acute cholecystitis, furthermore we are studying the preoperative examinations in connection with the operative findings and also the ways of avoiding complications.

Our opinion is that LC is worth choosing even in acute cases and not only the operative encumbrance is less for the patients but also the probability of postoperative complications is similar.

Is laparoscopic cholecystectomy with laparolift technique less invasive than open and pneumoperitoneum method?

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Surgical treatment is always connected with changes in homeostasis and tissue damage. The gold standard in gallstone treatment is cholecystectomy. In our work we have compared hormonal and inflammatory markers after three types of cholecystectomy: open, laparoscopy with pneumoperitoneum (12 mmHg) and gasless laparoscopy with laparolift (Origin) technique. These changes may have profound effects on metabolic and renal homeostasis, circulatory haemodynamics, immune competence and gastrointestinal physiology. It has some effects on patients' behaviour after surgery. Studies were performed on patients undergoing elective cholecystectomy. Patients were divided into three groups: open cholecystectomy 11 patients, laparoscopic with pneumoperitoneum 10 patients and with laparolift 14 patients. We examined levels of three catecholamines: adrenaline, noradrenaline and dopamine using HPLC-ECLD method, IL-6 and cortisol with immuno-enzymatic method and CRP with immunoturbidymetric method in patients' serum. Samples of catecholamines were taken before procedure, after anaesthesia but before surgical procedure half an hour after operation beginning, 2 and 24 hours after the end of procedure. Blood samples for IL-6 and cortisol were taken before operation, 6 and 24 hours after operation and for CRP before, 24 and 72 hours after operation. After our study we can conclude that hormonal response to surgical trauma after open procedure is higher than after two laparoscopic techniques. We have found no differences in two laparoscopic techniques in hormonal response. In laparoscopic technique with laparolift levels of catecholamine returns to levels before operation earlier than in open and laparoscopic with pneumoperitoneum method. Inflammatory answer is higher after open procedure than after both laparoscopic methods. We have found no differences after two laparoscopic methods.

Gasless laparoscopic surgery. Our perspectives based on an experience of more than 500 successive cases

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We perform gasless laparoscopic surgery routinely since 1994. Under this technique 515 successive operations have been carried out between January 1994 and July 1997, including cholecystectomies (one case with choledocolithotomy), Nissen fundoplication, vagotomies (posterior vagotomy and anterior seromiotomy or anterior linear gastrectomy, and truncal vagotomia and antrectomy), gastrenterostomy, treatment of hepatic cysts including bloc-resection of hydatid disease, splenectomy, cholectomies and gynecologic surgery (hysterectomies, anexectomies).

Results: Mean duration of surgery and hospital stay are similar (or better) to operations performed with CO_2 pneumoperitoneum. The conversion rate to open surgery was 3·3 per cent. Indications are referred. Major complications have been found only in seven cases consisting of duodenal injury, cystic duct leak, residual common bile duct stone, bile duct injury – diagnosed at the time of surgery and managed by primary repair over a

T tube) – duodenal stump leak and ureteral injury. A second operation was performed in five patients (1 per cent) for cystic duct leak, haemorrhage, duodenal perforation, duodenal leak and ureteral injury. There was postoperative shoulder pain in three cases.

Advantages of the procedure: an airtight pneumoperitoneum is not required; therefore we only use valveless trocars, conventional surgical instruments can be safely and routinely introduced, high volume irrigation is easily accomplished and continuous suction can be applied to the operative site without altering the exposure. The main problem is the difficult exposure in some cases, particularly in obese patients, which is solved by using an additional retractor.

Conclusion: Gasless laparoscopy is technically feasible, safe and effective, even in unselected patients, and it is a good route of choice for many different operations which can be routinely indicated for several reasons: it involves low complication and conversion rates, short duration of surgery, early postoperative discharge, and good functional and cosmetic results; it provides a good exposure and avoids the operative risk related to disturbances inherent to pneumoperitoneum; it makes postoperative should pain a rare complaint; it allows the use of conventional instruments, thus reducing the need of the disposable ones and making surgery easier and more cost-effective.

Endoscoic polipectomy as a preventive treatment of large intestine cancer

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A considerable increase in the number of large intestine cancers has been reported lately. Most of the cancers of this type are situated in polyps.

In the years 1988–1997 endoscopic polipectomy was performed in 184 patients, aged 23 to 80 years. The size of the removed polyps varied from 0·3 to 2·5 cm. There were 134 cases of a single polyp and 50 cases of numerous polyps (2–9 polyps per patient). Polyps were removed by means of diathermic loop or 'warm biopsy'. Macroscopic examination revealed benign lesions of adenomatous or tubular type in 176 patients, and adenocarcinomas in the remaining eight cases. All malignant polyps were larger than 1 cm. As the infiltration of the peducle was noted the surgery was performed in all eight cases. Postpolipectomic complications were recorded in three patients (1·6 per cent): two cases of arterial haemorrhage from the peducle of the removed polyps and one case of the simgoid perforation, which took place 26 hours after the surgery. All patients operated due to adenocarcinoma are regularly examined by means of colonoscopy in diagnostic cycles of 6, 12, 24 and 36 months. So far no cases of recidivation have been reported.

Conclusions:

1. Endoscopic polypectomy enables avoiding surgery in the case of benign lesion.
2. Early detection and removal of a polyp protects from its changing into a malignant one.

Postoperative pulmonary function after laparoscopic and open cholecystectomy

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Open cholecystectomy causes changes in pulmonary functions showing a restrictive pattern which can be related to respiratory complications of hypoxemia and atelectasis. Eighteen patients undergoing open cholecystectomy and 20 patients undergoing laparoscopic cholecystectomy, all in ASA I group, were prospectively evaluated by pulmonary function tests. Functional residual capacity (FRC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and forced expiratory flow (FEF 25 to 75 per cent) were measured before operation and on the morning after surgery to determine if laparoscopic cholecystectomy results in less respiratory impairment. The results revealed significant but less decreases in laparoscopic cholecystectomy (6, 23, 20, and 23 per cent respectively) than after open cholecystectomy (21, 36, 32, and 36 per cent respectively).

We conclude that laparoscopic cholecystectomy provides less impairment in pulmonary functions than open cholecystectomy. That may account for the reduced rate of respiratory complications after laparoscopic cholecystectomy.

Foreign body removal – a problem for endoscopy rather than for surgery

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Foreign bodies are in the majority of cases the results of self-injury of prisoners. Most of the foreign bodies are metal or wooden cross-like, self-expanded structures (two wires bound in the middle with a piece of elastic) with sharp ends. When swallowed, the objects create the risk of oesophagus wall perforation and the injury of big vessels. Most of the patients operated on due to foreign bodies in the alimentary canal undergo this type of intervention repeatedly. In the years 1994–1997, 39 attempts were done to remove foreign bodies from the oesophagus by means of endoscopy. The patients were men, aged 17–35 years. In each case a contrast X-ray of the oesophagus was done before the endoscopy to exclude the wall perforation. In 16 patients the cross-like foreign bodies expanded and stacked in the second isthmus of oesophagus. In 23 cases they were held up over the cardial part of the oesophagus. Thirty-three endoscopic interventions were performed in local anaesthesia, 16 in general anaesthesia. Foreign bodies were satisfactorily removed from the oesophagus in 30 cases. A typical intervention started with cutting the elastic that bound two arms of the cross. Then each arm of the cross was removed separately with the use of diathermic loop. In eight cases the arms were removed from the inflammatory infiltration of the oesophagus wall and no cases of wall perforation were noted. In nine patients an attempt to remove a foreign body from the oesophagus was unsatisfactory due to technical difficulties. Foreign bodies were removed surgically by means of thoracotomy (2 cases), gastrotomy (3 cases), and through the cervical access (4 cases). Before gastrotomy the foreign body was endoscopically introduced into the stomach. Endoscopic removal of foreign bodies from oesophagus is a very difficult procedure. It is especially recommended for those patients who swallow some foreign bodies repeatedly. If performed satisfactorily, the method lets us avoid an extensive surgery burdened with the risk of intra- and postoperative complications. The endoscopic intervention should be performed by a surgeon-endoscopist, who, if necessary, could convert to surgery.

Laparoscopic Heller myotomy and fundoplication for achalasia

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Introduction: In spite of the fact that pneumatic dilation of the cardia in achalasia offers some acceptable results not exempt of risks, dysphagia, although diminished, usually reappears during the first months. So, laparoscopic Heller myotomy associated with a Dor fundoplication, with or without previous dilation, is in our opinion the definitive treatment for achalasia.

Patients and methods: Between January 1995 and July 1997, 8 consecutive patients were treated. Three of them had a previous pneumatic dilation only temporally successful. The preoperative manometries showing a LESP from 36 to 12 mmHg and aperistalsis supported the diagnosis of typical achalasia with a case of vigorous type. The surgical technique was similar in all patients but nowadays the hiatus dissection is limited, preserving the posterior attachment. Five trocars of 10 mm were used. There were dissected at least 7 cm of oesophagus, identifying and preserving later on while the myotomy the anterior vagus. The myotomy was carried out with scissors and electrocoagulation, maintaining an intraeoesophageal bugie of 40F, beginning 2 cm below the gastroesophageal junction. We used the cardial artery as anatomical reference. The myotomy is prolonged upwards in about 6 cm testing by intraoperative endoscopy its completion and the absence of perforation We associated a partial fundoplication Dor type to avoid the gastroesophageal reflux In a case, with previous balloon dilation, a microperforation was identified and sutured without postoperative complications. Mean operative time was 130 min The postoperative stay was between three and six days

Results: Only four cases have a follow-up longer than one year All cases but one are asymptomatic without dysphagia or gastroesophageal reflux A case has deglutory problems secondary to the oesophageal aperistalsis with a LESP of 3·5 mm Hg and a correct Heller myotomy in endoscopy

Laparoscopic splenectomy

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Introduction: Nowadays autoimmune hereditary anaemias (AIHA) and idiopathic thrombocytopenic purpura (ITP) with poor response to steroid treatment are the more frequent indications for splenectomy Laparoscopic splenectomy offers the advantage of minimal invasion and seems to be an attractive alternative.

Patients and methods: Between September 1994 and June 1997, 18 consecutive patients, 17 female, with ages between 12 and 71 years underwent laparoscopic splenectomy Indications for splenectomy were medication resistant ITP in 11 cases, AIHA in four, spherocytosis in one, thrombotic thrombocytopenic purpura (TTP) in one and splenic cyst In patients with ITP the platelet count ranged between 9000 and 3600 mm^3 In all cases high-dose immunoglobulins and pneumococcal vaccine were given before the operation. After the administration of high-dose immunoglobulins the platelet count raised, and ranged between 60 000 and 140 000 mm^3. Preoperative sonography showed a mean splenic length of 12 cm and no accessory spleens were detected. The surgical technique was always similar, using four ports as described in other communication

Results: The length of the operation ranged between 135 and 210 min Laparoscopic splenectomy was successfully performed in 17 cases One conversion was necessary because uncontrollable but non-important bleeding (the second case) In one case was necessary to reoperate the patient in the postoperative period. In one case, injury to a sizeable vessel was controlled by laparoscopy. Accessory spleens were searched for systematically It was found in one patient (not showed previously in sonography) and removed successfully In 15 cases the postoperative course was uneventful One patient had a small subphrenic collection resolved in 7 days without drainage The postoperative stay ranged between 2 and 9 days (median of 3 days) In the patients with ITP the postoperative mean platelet count was 230 000 mm^3 (range 125 000–430 000 mm^3)

Comments: The laparoscopic approach has demonstrated to be as effective and safe as the open, also to localize ectopic spleens.

Diagnostic and operative laparoscopy in diagnosis and treatment of selected acute abdominal diseases

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Aim: Aim of the study was to evaluate how the laparoscopic technique may improve a diagnosis and enable a treatment of common acute abdominal diseases.

Material and methods: 157 patients (72 women and 85 men) qualified for laparotomy were laparoscopized. Appendicitis was suspected in 88 cases, in the rest (69 cases) – acute cholecystitis Mean age was 53 years Then we performed a laparoscopy and (if possible) a definite treatment was done.

Results: In the group suspected of appendicitis the accuracy of diagnosis was 75 per cent. Other findings were. cystis ovarii ruptum (20·4 per cent), pyosalpings (3 5 per cent), and tumour coeci (1 1 per cent). Mean appendectomy time was 42±21 min Conversion rate during appendectomy was 9 1 per cent (6 cases) Conversions were performed because of hard inflammation of caecum, anatomical doubts and some technical troubles. Complications of laparoscopic appendenctomy: perforation rectum due to diathermy (1 case), intraabdominal collection (2 cases). No wound infection was noted Mean hospital stay was 4±3 days In the group suspected of cholecystitis the accuracy of the diagnosis was 98·6 per cent In one case (1 4 per cent) perforation of duodenal ulcer was found Mean cholecystectomy time was 66 4±28 min Conversion rate during cholecystectomy was 11 8 per cent (8 cases) Main reasons were anatomical doubts – 4 cases, inflammatory inflammation – 2 cases, bleeding from hepatic lodge – 2 cases. Complications noted wound infection (1 case), biliar peritonitis (1 case), duodenal perforation (1 case), intraabdominal abscess (2 cases). Mean hospital stay was 4 5±3·2 days

Conclusion: Laparoscopy and laparoscopic operative technique may be very useful in many – especially difficult – cases of local peritonitis. In a few cases this technique enables a final treatment of the disease

Laparoscopic cholecystectomy (LCh) in the cirrhotic patients

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Purpose: Liver cirrhosis is a serious surgical risk factor because of the patients' general condition and certain technical difficulties due to rich collateral circulation and bleeding tendency Simple cholecystectomy might become a serious surgical problem

Methods: Sixteen cirrhotic patients underwent LCh because of the gallstone disease According to the Child–Pugh classification 7 patients were in A group, 8 in B and 1 in C (waiting for OLT) Each patient was prepared with special care to assess his liver function and bleeding tendency profile In five patients with the sonographic evidence of the CBD stones, LCh was preceded by ERCP and in three cases the stones were found and removed The Child C patient (with CBD stones and cholecystitis) was prepared with 4 units of plasma transfusion prior to ERCP and next 4 units before LCh in order to prevent coagulation disorders. In 11 cases LCh was an elective procedure, in five cases a delayed emergency procedure.

Results: LCh was performed safely and successfully in all patients. In three cases a moderate bleeding from the gallbladder lodge was effectively controlled by spongogel placement and 2 units of plasma transfusion Drainage of the gallbladder lodge were done in all the patients The average time of the intervention was longer than that in non-cirrhotic patients. No case of postoperative bleeding, liver failure or other complications was observed The average hospitalization period was 5 days (3–7 days)

Conclusions: Our experience suggests that LCh in the cirrhotic patients is an effective and safe alternative to open cholecystectomy

Endoscopic polypectomy of the lower part of gastrointestinal tract in own material

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The data present own experiences and analysis of colonoscopic examinations of the lower part of gastrointestinal tract with special consideration of endoscopic polypectomy. In the period of time from 1984 to 1997, 1512 colonoscopic examinations have been done On 344 cases endoscopic polypectomy have been done. The polypectomies in 90 per cent were performed in outpatients department.

Patients were prepared with special kind of diet (for 3 days they have had only jelly and drinks)

All removed polyps were histopathologically examined. In two examined polyps the carcinoma diagnosis was established. We experienced 5 complications – 4 bleedings and 1 perforation. All patients are well and disease free 3 and 6 months after polypectomy.

In our opinion this model seems to be an easy and safe method of colon polyps treatment. Simultaneously it is an efficient method in prevention of colon cancer.

Metabolic and immune response to operative trauma during laparoscopic and open cholecystectomy

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The aim of the study is the comparison of metabolic changes and the concentration of acute phase protein changes caused by the intraoperative trauma during laparoscopic cholecystectomy (lch) and open cholecystectomy (lch). The examination was carried out in 90 patients having an operative treatment because of non-complicated cholecystolithiasis between 1994 and 1997. The laparoscopic method was used in 60 patients including 40 women and 20 men at the average age of 47. Open cholecystectomy was carried out in 30 patients, including 22 women and 8 men at the average of 42. The concentration of C-reactive protein (CRP), component C3 of the complement, immunoglobulins G, A, M, fibrogen, glucose, sodium, kalium and leucocyte count were determined in blood sampled 24 hours before the operation and 4, 24, 48, 72 and 96 hours after the operation. The dynamics and the range of temperature changes of the patients bodies in the perioperative period were examined as well. The highest concentration of CRP was recorded in both groups 48 hours after the operation. After lch concentration of CRP increased four times and after och 14 times. On the second and third day after the operation concentration of CRP gradually decreased. Statistically significant changes in C3 concentration were not found in both groups of examined patients. The observed decrease in immunoglobulin concentration was similar after lch and och. The increase in fibrinogen concentration proceeded within the normal range and on the first day equalled 45 per cent of the perioperative value for lch and 60 per cent for och. On the operation day the increase in glucose concentration of 0·5 mmol/l, leucocyte count of 1·8 g/l, sodium concentration of 6·9 mmol/l, and the decrease in kalium concentration of 0·4 mmol/l on average were observed after lch. The increase in glucose concentration of 1·9 mmol/l, leucocyte count of 5·3 g/l, sodium concentration of 6·4 mmol/l and the decrease in kalium of 0·6 mmol/l were observed after och on the operative day. Lesser disturbances in aggressive metabolism and lesser concentration of acute phase proteins are observed after lch. It is related to the lesser intraoperative trauma in comparison to och. The numerous clinical advantages result from lesser intra- and postoperative stress.

Routine compared with non-scheduled follow-up of patients with 'curative' surgery for colorectal cancer

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Background: The main rationale for follow-up of colorectal cancer patients resected for 'cure' is that early detection and treatment of recurrence and metachronous disease should result in improved survival. Our purpose was to assess in a prospective fashion the impact on survival of a follow-up program vs that of undergoing non-scheduled visits.

Methods: From 1980 through 1993, a prospective study was carried out on 800 patients with colorectal adenocarcinoma radically resected with no evidence of synchronous cancers of the colon and rectum or in other organs, of whom 322 patients were to attend a 5 year follow-up, and 478 patients were free to make non-scheduled visits on account of symptoms.

Results: Asymptomatic recurrence was found at follow-up in 92 (28 per cent) of 322 patients, whereas 175 (36 per cent) of 478 patients had a symptomatic recurrence detected at a non-scheduled visit. Diagnosis of resectable recurrence was established within a median time of 21·5 months. Surgical resection of recurrence was performed in 30 (32 per cent) of 92 and in 13 (7 per cent) of 175 patients (32 vs 7 per cent; $P<0{\cdot}001$). Resection was curative in 13 (14 per cent) of 92 and in two (1 per cent) of 175. Five year survival of resected recurrence as 10 per cent in 30 of 92 patients and 0·8 per cent in 13 of 175 (10 vs: $P<0{\cdot}01$). Two patients are alive with no evidence of disease or two (2 per cent) of 92. Metachronous colorectal lesions were treated for cure in 63 (19·5 per cent) of 322 patients. The effectiveness of scheduled follow-up was 4 per cent (13 of 322 patients).

Conclusion: These results underline the rationale for a follow-up programme in early detection and surgical treatment of recurrent disease in patients operated on for colorectal cancer.

111-In labelled antibodies in the detection of colorectal carcinomas

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Oncoscint CR 103 is an immunoglobulin which recognizes a tumour-associated glycoprotein (TAG-72) expressed in several cancers of epithelial origin, including colonic adenocarcinomas. The aim of the study is detection of the recurrences and metastases of colorectal carcinomas using 111-In labelled antibodies B72.3.

Fourteen patients have been examined (13 with adenocarcinomas of caecum, colon and rectum and one with squamocellular colonic carcinoma) from 4 months till 2 years after surgery, two of them after 2 months after the end of radiotherapy. Radiochemical purity of the radiopharmaceutical was over 97 per cent. Planar anterior, lateral and posterior scintigrams of thorax, abdomen and pelvis are done after 10 min, 24, 72 and 96 h after i.v. injection of Oncoscint CR-103, containing monoclonal antibodies B72.3 labelled with 150 MBq 111-In while tomographic scintigrams of the pelvis are done after 72 h.

In 12 patients recurrences of carcinomas (5–12 cm), in six recurrences with liver metastasis, and in two only liver metastases were detected and confirmed by surgery. Planar immunoscintigraphy was positive in 8/8 patients with liver metastases and 9/14 patients with recurrences while in 5/14 recurrences were detected only by tomography. US patients with recurrences, while MRI in one. In three patients with recurrences, CEA was not increased. In four patients intensive accumulation of labelled antibodies was observed in colostomas, in one with granuloma, as well as in one with recurrence of squamocellulare carcinoma.

We can conclude that with tomography, we can access better distinction of tumour in comparison to other structures and estimation of its size. Other imaging methods (CT, US) have advantage in detection of liver metastases, while immunoscintigraphy is more specific for the assessment of malignant abdominal tumours and extrahepatic metastases. The first results point out that Oncoscint CR-103 can be useful in diagnosis of recurrences and metastases of colorectal carcinoma, viability assessment after radiotherapy and in the choice of the adequate surgical treatment in dependence of the spread of the disease.

Changes in colorectal surgery at our department during a 10 year period

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We have performed 612 colorectal operations during the investigation period of 1988–1997. This 10 yerar period was divided into two 5-year periods (1988–1992 and 1993–1997) and we have compared mortality rates, operation types and suturing technique in acute and elective surgery.

In acute surgery we have found a decrease in the number of 2 or 3-phase surgical interventions and a decrease in mortality rates (24 per cent during the first period and 15 per cent during the second one) due to tendencies to primary definitive care (extended resections, intraoperative bowel irrigation).

In elective surgery of mid and lower third rectal tumours the number of sphincter saving operations increased, staplers were used more frequently (the ratio of stapler and hand made sutures in the first period was 2/3 and 4/1 in the second one) and suture insufficiency occurred at a lower rate during the second period, beside similar mortality rates (1·3 per cent).

Prediction of complications after colorectal surgery using gastric tonometry and cytokines

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Aim: We have estimated the value of gastric tonometry and IL6 and TNFα in prediction of complications after elective colorectal surgery in a prospective randomized study involving propofol and epidural anaesthesia.

Materials and methods: A significant advantage has already been shown in patients having an epidural, being associated with shorter operations (median 126, range 60–280 mins vs 180, range 86–240; $P<0{\cdot}01$), less blood loss (median 710, range 200–2235 ml vs 1325, range 250–2725; $P<0{\cdot}05$), better pain relief (83 per cent vs 37 per cent; $P<0{\cdot}02$) and a tendency to return home earlier.

Results: Only IL6 levels predicted postoperative complications (day 1; 200, range 72–600 pg/ml vs no complications 97, range 0–595; $P<0{\cdot}002$). No similar association was found with TNFα. There was a fall of gastric mucosal pH during operations (median fall of pH 0·08) but this had no relation to type of anaesthesia, blood loss, length of operation or the development of postoperative complications.

Conclusion: Plasma levels of IL6 can predict surgical complications after elective colorectal surgery but gastric tonometry was unhelpful, which probably reflects good intraoperative anaesthetic practice.

A simple method to determine the length of bowel resection in the presence of colonic ischaemia

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It is well known that necrosis due to colonic ischaemia of the mucosa is greater than of the serosa. The surgeon must always resect a piece whose length is greater than the area of identifiable necrosis but it is always difficult to determine the exact resection margins.

Ojective: Obtain a simple and practical method to determine the length of bowel resection when there is a transmural necrosis of the colon.
Material and methods: Organs from 46 human cadavers were used. The marginal arterial arcade (marg. arc.) was resected: 5 cm in 17 cases (group I); 8 cm in 17 cases (group II); 12 cm in 12 cases (group III). The organs were then injected via the *arteria mesenterica inferior* and studied using the following techniques: diaphanization (42); microangiography (6/42); scanning electronic microscopy of corrosion casts (4).
Results: The colon in the site of the devascularization presents: 1) *Group I* – in 73·3 per cent of the cases the serosa shows a decrease of its colour with an average length of 1·7±0·18 cm. The area of discoloration of the mucosa is 29·4 per cent or 88·2 per cent greater than the discoloration of serosa at the free colonic and mesocolonic borders respectively; 2) *Group II* – in 53·3 per cent of the cases the serosa shows a discoloration with 2·8±0·37 cm. The area of the discoloration of the mucosa is 28.6 per cent or 82·1 per cent greater than the discoloration of serosa at the free colonic and mesocolonic borders respectively; 3) *Group III* – in 100 per cent of the cases the serosa shows a disocloration with 5·3±0·43 cm. The area of the discoloration of the mucosa is 39·6 per cent or 83·0 per cent greater than the discoloration of serosa at the free colonic and mesocolonic borders respectively.

To the above percentages we added the number 1 (i.e. 1·294; 1·882; etc.) and then rounded off to the decimal, obtaining in this manner values 1·3–1·4 and 1·8–1·9. We classified these numbers *minimum* and *maximum* quantification indexes of the mucosal ischaemia, respectively. The diaphanization, microangiography and scanning electronic microscopy showed that the discolorations represent a proportional decrease of the product inside the vessels.
Conclusions: In cadavers, the devascularization seems to reveal that the ischaemia of the mucosa at the level of the free colonic border is 1·3 to 1·4 times greater than what is observed at the surface of the bowel, and increase to 1·8 to 1·9 at the level of the colonic mesocolonic border. We propose to name those values by *minimum* and *maximum* quantification indexes of the mucosal ischaemia, respectively. These simple and practical numbers can help surgeons evaluate the length of the mucosal lesion. In order to determine bowel resection margins the surgeon needs only to multiply the index value by the area of ischaemic visible on the serosa.

Multiple colon tumours. Diagnosis and follow-up of 600 patients with colorectal carcinoma

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Aim: Failure to diagnose synchronous tumours leads to error in patient treatment and prognosis. The existence of metachronous tumours requires strict patient follow-up to ensure early identification of the second tumour. The present study evaluates the results obtained with a structured protocol for diagnosis and follow-up of multiple colorectal carcinoma.
Materials and methods: A structured procedure was used to follow for 6 years (from 1991 to 1997) a group of 15 patients (2·5 per cent) with multiple colorectal tumours (7 synchronous and 8 metachronous) of a series of 600 colorectal neoplasms. Synchronous tumours were those which appeared within 6 months after the initial diagnosis, with mucosa appearing healthy during the interval between detection of the two tumours. Metachronous tumours were those found later than 6 months after diagnosis of the first tumour. Nine patients were men and six were women with a mean age of 67 years (range: 45–83). The disease was staged according to the system of Astler-Coller. Postoperative examinations consisted of colonoscopy one month after surgery if the preoperative examination was incomplete, serum carcinoembryogenic antigen (CEA) every three months, and complete annual check-up (clinical examination, laboratory tests, chest X-rays, ultrasound or tomographic liver study, CEA, colonoscopy and pelvic tomographic studies in rectal cancer).
Results: Six synchronous tumours were diagnosed preoperatively and one intraoperative. Of the eight metachronous tumours, seven strictly adhered to the follow-up protocol, as a result of which the second tumour was detected at an early stage. The remaining case involved no follow-up, and the second tumour was diagnosed in an advanced stage as a result of bowel obstruction. The left colon was predominantly involved; polyps were detected in 10 cases while two patients had three malignancies detected by histopathological study.
Comments: We emphasize the need for a full evaluation of the colon in all patients with colorectal carcinoma. In the case of incomplete preoperative evaluation, intraoperative colonoscopy is to be considered; if this is not feasible it should be performed one month after surgery. A structured follow-up procedure permits early detection of these tumours, thereby improving patient prognosis.

The methods of surgical treatment of total large bowel obstruction

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Aim: Aim of this study was to evaluate effectiveness of the on-table large bowel antegrade irrigation and Hartmann's procedure in totally obstructed left sided large bowel carcinoma.
Materials and methods: Data of the 60 patients were collected prospectively without randomization. Hartmann's procedure was performed in 49 patients, and irrigation and primary anastomosis in 11 patients. Irrigation was done as described by A.G. Radcliffe (1983).
Results: Two groups of the patients have shown no differences in age, sex, carcinoma TNM stage and morbidity and morality postoperative rate. Mortality was 20·4 per cent (10 patients) in Hartmann's operation group to compare with 18·2 per cent (two patients) in irrigation group. There were no specific intraoperative complications which could be attributed to irrigation, but two cases of anastomatic leakage were recorded. One case was treated conservatively, but another was reoperated and died of septic complications. In irrigation group, of course, there were no colostomy complications, in the other group 12 patients were noted with complications. Only statistically significant difference was found in duration of the hospitalization. In Hartmann's op. group it was 24·1±15·3 days, to compare with 16·6±8·0 days in irrigation and primary anastomosis group ($P<0·05$).
Conclusion: It was concluded, that on-table large bowel irrigation is convenient, safe and economically reasonable procedure in treatment of the obstructing left sided carcinomia of the large bowel. Nevertheless, it is related with high morbidity and mortality. The preoperative recanalization of the tumour can be the way of solution of this problem.

Respects of antibiotic therapy in elective surgery of colorectal carcinoma

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Aim: Authors evaluate the results of the elective resections of the colon because of colorectal carcinoma between 1991 and 1997. The methods and the effectivity of the antibiotic profilactical therapy were also studied.
Patients and methods: In this period 488 operations were performed, 374 cases of them had elective operations (76·6 per cent). The patients mean age was 64·5 (26–94), male–female rate was 1·2:1. Before all of the interventions the patients had preoperative mechanical preparation of the colon. In the last 4 years cefetoxime, metronidazole antibiotic treatment was used as profilaxis. The surgical methods were the following: in 202 cases different types of resection of the colon (54 per cent), anterior rectum resection in 58 cases (15·5 per cent), abdominal perineal extirpation of the rectum in 57 cases (15·3 per cent), gastrointestinal bypass operation in 15 cases (4 per cent), definitive colostomy in 42 cases (11·2 per cent) were performed.
Results: The used antibiotical profylaxis treatment was effective, the rate of the insufficiency of the anastomoses was lower with 1·6 per cent, the suppuration was lower with 2·4 per cent than the former used antibiotics. The mortality in 30 days was also lower with 1·6 per cent than before. Comparing the simple and multiple doses of antibiotic therapy significant difference has not been found in the results of our operations.

Conclusion: On the base of our results the preoperative mechanical preparation of the colon together with the combination of cefetoxime, metronidazole antibiotic profilactical therapy is an effective treatment for the preparations of the patients.

Immunocytochemically detectable metallothioneins in chronic ulcerative colitis

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Introduction: Metallothioneins (MTs) are a set of low-molecular weight proteins with a high binding affinity for heavy metal ions. MTs have been shown to be potential scavengers of oxygen derived free radicals occurring during inflammatory processes Furthermore a possible cytoprotective role for circulating MTs has been demonstrated in chronic gastric ulceration
Aim: The aim of the present study was to investigate whether immunohistochemical MTs expression in ulcerative colitis (UC) is associated with the activity of disease and whether MTs have a cytoprotective role.
Materials and methods: MTs expression on routinely processesd colectomy specimens from 48 patients with UC was immunohistochemically demonstrated by means of the monoclonal anti-MT antibody E9. MTs expression was although examined in histologically normal uninflamed colonic mucosa of 10 patients who underwent colectomy for colon cancer
Results: In colon cancer specimens with normal appearing mucosa no MTs expression was observed In UC a strong MTs overexpression in intestinal epithelial cells was seen in 14/48 specimens and in a moderate in 9/48 without correlation to degree of inflammation. MTs overexpression was although found in fibromyoblastic spindle cells at the base of almost all ulcers observed.
Conclusions: MTs overexpression in fibromyoblastic spindle cells of ulcerative lesions indicate a possible protective role of MTs in the inflammatory process (binding protein for free radicals). On the other hand immunohistochemically MTs expression does not seem to be an indicator of disease activity in UC

Total proctocolectomy and ileoanal anostomosis with ileal J-pouch

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Ileoanal anostomosis with ileal J-pouch that has been done with proctocolectomy operations prevents patients from the physical and psychological damages of permanent ileostomies

In between the years 1989 and 1997, total colectomy + mucosal proctectomy + ileoanal anostomosis with ileal J-pouch (with protecting loop ileostomy) operation had been performed to 18 patients with stapling technique in our clinic. Preoperative diagnosis of five patients (all are male and ages range between 31 and 58) was ulcerative colitis In 11 patients the preoperative diagnosis was poliposis coli (8 male, 3 female and ages range between 18 and 42). And two patients had familial poliposis (father and sister, ages 45–21) In two patients with poliposis coli, differentiated adenocarcinoma had been detected pathologically at postoperative period In all patients protecting ileostomy was closed 8 weeks after operation.

After the operations, in one patient anal structure and anostomotic leakage developed in early postoperative period, then leakage and stenosis were improved by reoperation In one patient anal incontinence developed postoperatively but this was improved with anal exercises by 2 months In one patient pouchitis had been developed and this problem was overcome with medical treatment (morbidity is 16 66 per cent) In one patient pouchitis had been developed and this patient died because of this complication at 10th postoperative day (mortality is 5·5 per cent) One patient died at postoperative 16th month because of biliary cirrhosis. All other patients are under follow-up and well by today. The mean defecation habit is 4–7 times a day 3 months after operation

We conclude that total proctocolectomy + ileoanal anostomosis with ileal J-pouch operation is a good procedure of choice to save the patient's comfort with acceptable ratios of morbidity and mortality.

Colon schwannoma. A exceptional case report

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Introduction: Neurogenic tumours originate on peripheral nerves, where they may or may not be associated with Von Reckinghausen neurofibromatosis Although they are more frequently found on the acoustic nerve (acoustic neurilemoma), and only rarely found in the digestive system, there mostly in the duodenum, they are only exceptionally found in the colon.
Case report: This is the case of a 75-year-old female patient with a clinical history of asthenia, anorexia and slight weight loss High level of anaemia (5 9 g of haemoglobin and 19 per cent of haematocrit). In the study of this anaemia a colon repletion defect is observed in contrast enema; a colonoscope reveals an ulcerated mass 45 cm from the anal margin which biopsy reports as a schwannoma Surgical intervention follows, revealing a tumour of 6 cm in diameter occupying the sigmoid colon and ulcerating the mucosa. A sigmoidectomy is carried out, with mechanical anastomosis The definitive study from pathological anatomy reports a benign schwannoma with predominance of A-Antoni areas. Evolution is satisfactory with later tests giving normal results
Comments: Presence in the colon is exceptional, and international medical literature does not describe any such case, leading to the elaboration of this report. Digestive schwannomas or neurilemomas present a long and concealed clinical history, with anaemia arising from digestive haemorrhage when the tumour ulcerates and necroses leading to the diagnosis. Generally benign, they originate in the Schwann cell. Treatment is intestinal resection

Vascular ectasias of the right colon

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The aim of this study is to indicate the diagnostic and operative problems in managing patients suffering severe haemorrhage due to angiodysplasia (more accurately termed as vascular ectasia) of the right colon.

During the last decade six patients aged 62 to 82 years old required urgent laparotomy for lower gastrointestinal bleeding Preoperative emergency colonoscopy, as the first choice diagnostic procedure, was performed in all patients By way of colonoscopy it was feasible to distinguish whether the bleeding originated from the left or right colon. In one patient, it was impossible to distinguish the source of bleeding because of the coexistence of angiodysplasia in both right and transverase colon. The preoperative diagnosis which was performed by inferior mesenteric arteriography was accurate for vascular ectasias in three patients

Five of our patients had had right hemicolectomy, although the sixth one had a near total colectomy (the patient with the two synchronous angiodysplasias). No recurrence of the haemorrhage occurred during the immediate postoperative period The final diagnosis was made by the histopathological studies of the specimens

Vascular ectasias of caecum and ascending colon are important vascular lesions responsible for rare but severe lower gastrointestinal haemorrhage in elderly patients The main problem in treating such patients is to obtain accurate preoperative diagnosis, in order to proceed to the proper surgical technique. In cases with no certain arteriographic nor colonoscopic diagnosis, the choice of right hemicolectomy usually solves the therapeutic problem

Immunological state and erythropoietin (EPO) response in colorectal cancer

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Aim: Apparently, cytokines are involved in all of the major aspects of the pathogenesis of anaemia of chronic disease, namely inhibition of the proliferation of erythrocytic progenitors, impaired availability of iron, and lowers blood of EPO (W.E. Jelkmann, Annals New York Acad Sci 1994). For this motive we want to investigate immunological parameters and EPO levels in colorectal cancer patients.

Materials and methods: Following institutional ethics committee approval from University Hospital of Valladolid and informed consent of patients, TCD8, TCD4 and B lymhocytes, NK cells, immunoglobulins (Ig) G, M and A, the IL-2 receptor (RIL-2), haemoglobin (Hb), haematocrit (Ht) and EPO levels were measured in blood. We have compared these parameters in a group (Group 1) colorectal-cancer patients (n=20) vs a group of healthy people (n=20). The colorectal-cancer diagnosis was performed by colonoscopy with biopsy. All blood-specimen were taken before surgery. Statistical analysis of data was performed using ANOVA of repeat measurements and the Scheffé-test and the Pearson-correlation test, with significance documented at the P<0·05 level.

Results: Groups were comparable in terms of anthropometric characteristics. Results are shown in the following tables:

	Group 1	Group 2	Significance
TCD8 cells (%)	32·8±11	36·6±11	NS
TCD4 cells (%)	39·8±10	40·9±10·2	NS
B cells/ml	7·6±4·8	8·1±3·4	NS
NK cells (%)	22·1±12·7	19·1±10	NS
Ig G (UI/ml)	124·7±33	146·1±31·6	NS
Ig M (UI/ml)	171±70·7	176±69·4	NS
Ig A (UI/ml)	199·5±89·6	199·5±89·6	NS
RIL-2 (pM)	86·6±32·2	57·6±28	P<0·01

	Group 1	Group 2	Significance
Hg (gr/dl)	12·2±2·6	15·5±1·2	P<0·01
Ht (%)	38·8±6·7	46·3±3·4	P<0·01
EPO (mUI/ml)	20±5	8·6±3·1	P<0·01

We have found a significant correlation (r=–0·59, P<0·01) between the EPO-levels and hemoglobin in group 1, but none in group 2.

Conclusions: We conclude that EPO levels are inappropriately high in colorectal patients, in the early stage of diagnosis and this increase was correlated with haemoglobin levels. What can indicate an incipient anaemia or one must to consider it as a global event of the colorectal cancer.

Fluorouracil and high-dose leucovorin with radiotherapy as adjuvant therapy for rectal cancer. Results of a phase II study

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Aim: The purpose of this phase II study was to evaluate the efficacy and toxicity of fluorouracil and high-dose leucovorin (5-FU/LV) with pelvic irradiation as adjuvant therapy for patients with macroscopical resected rectal or rectosigmoid cancer.

Material and methods: Following surgery for stages II–III primary (52) or recurrent rectal cancer (4), 56 patients received eight cycles of 5-FU/LV and pelvic irradiation. 5-FU doses were 200 mg/m^2 for cycles 2–3 and 300 mg/m^2 for cycles 1 and 4–8. LV doses remained fixed at 200 mg/m^2. Pelvic radiation was started in third week, between the first and second cycle. The total dose was 50·4 Gy.

Results: No severe complications had been recorded. The incidence of grade 3 diarrhoea was 19 per cent. Three patients presented leukopenia grade 3 (5 per cent). In 44 patients (78 per cent) the planned treatment could be administered. The median follow-up was 40 months (range 22–66). Seven patients had local relapse (13 per cent) and six developed distant metastasis (10 per cent). The three years disease-free survival was 72 per cent and the overall survival was 76 per cent.

Conclusions: These preliminary results show that combined postoperative 5-FU/LV and pelvic radiotherapy are well tolerated and present a reasonable local and survival rates. This adjuvant treatment should be evaluated in randomized trials.

Histopathological prognostic score in colorectal adenocarcinomas

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Aim: To evaluate the predictive value of p53 protein expression in gastric adenocarcinomas.

Material and methods: Eighty-nine patients operated on for gastric adenocarcinoma were included, all of them underwent curative gastrectomy (stages I, II, III of the Japanese Staging System). Immunohistochemical p53 protein expression was assessed in formalin-fixed paraffin-embedded tissue samples from the primary tumours (CM1 antibody). Relationship between p53 expression and histological type (Lauren classfication), depth of tumour infiltration in gastric wall, presence of lymph node metastasis and proliferative activity (PCNA labelling index). The relative importance of each factor on the risk of death was assessed by Cox's regression analysis.

Results: Thirty-three (37 per cent) tumours showed positive nuclear immunostaining and overexpressed p53 protein. Diffuse carcinomas were significantly more frequently p53-positive than intestinal carcinomas (44·6 per cent vs 24·2 per cent) (P=0·02). Tumours with high PCNA labelling index (>50 per cent tumour cells showing immunoreactivity) exhibit more frequently p53 positivity than tumours with low-moderate PCNA index (P=0·08). No relationship was detected between p53 immunostaining and staging, tumour site, depth of tumoral invasion in gastric wall and lymph node metastases. Thirteen (39·4 per cent) patients with p53-positive tumours and 11 (19·5 per cent) p53-negative tumours (P=0·02) died due to the gastric cancer. Cumulative probability of survival at 36 months after surgery was lower in p53-positive tumours (50 per cent vs 72 per cent) (P=0·01). Survival in stages II and III was lower for patients with p53-positive tumours (40 per cent vs 62 per cent) (P=0·03). P53 protein showed significantly independent predictive value in the multivariate analysis variables. The risk of death due to gastric cancer was 2·22 times higher (95 per cent CI: 1·1–4·47) in patients with tumours that showed overexpression of p53 protein.

Conclusion: Overexpression of p53 protein is a negative predictive factor, associated with lower survival, in patients operated on for gastric cancer. This test may be an aid to standard staging classifications for the identification of subpopulations with different prognosis.

Complications of ileal and colonic loop reconstruction during and following radical cystectomy

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Complications during and following radical cystectomy and intestinal (ileal or colonic) loop or pouch operation performed in a total of 30 patients with Transitional Cell Ca during 1995–1997 by 2nd Urology and

2nd General Surgery Departments have been retrospectively evaluated in this study

Of these 30 patients undergone ileal or colonic loop/pouch, the mean age was found to be 57 3 years ranged between 30 and 72 years. The percentages of males and females were 89 4 and 11 6 per cent, respectively

In 23 patients, a free ileum segment that was 15 cm long with due protection of vascular band has been prepared and intestinal continuity was provided with end to end ileo-ileostomy In six patients, beginning from the proximal of the rectosigmoid junction a free sigmoid segment with 15 cm length has been prepared and continuity was provided with end to end colo-sigmoidostomy In one patient special Indiana Pouch that contains terminal ileum and coaceum has been prepared

In two patients to whom ileal loop has been prepared, an obvious vascular deficiency was observed at the line of anastomosis during operation Therefore, resection and reanostomosis were made. In another patient to whom colonic loop has been prepared an iatrogenic rectum injury that occurred at the time of prosthatectomy was corrected and a proximal protective loop colostomy was performed In a total of three patients a postoperative evisceration was developed and a second operation was needed for the correction. In 10 (33 0 per cent) out of 30 patients, there were some of the signs of intestinal obstruction during early postoperative period. This situation persisted for 3–6 days and they were only medically treated (correction of fluid and electrolyte balance, nazogastric decompession, early mobilization) Interestingly, none of them required a second look surgery.

Emergency colonic resection with anastomosis for diverticular disease and carcinoma complicated by peritonitis

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Advances in surgical techniques and intensive care medicine have recently renewed the interest on the one stage treatment of diverticular disease and colonic carcinoma complicated by peritonitis The aim of this study is the evaluation of results of colonic resection with immediate anastomosis after these surgical emergencies

At our institution, one surgical team well trained in colorectal surgery performed a colonic resection with primary anastomosis in 19 patients (mean age 65 years, 30–90 years) with peritonitis. Seventeen patients (89 5 per cent) had ASA stage superior than II. The peritonitis was due to diverticular disease in 11 cases (58 per cent) and to colonic carcinoma in 8 (42 per cent) Five carcinomas were situated in the right colon and three in the left colon. According to the Hinchey's classification, the peritonitis was stage I in 13 patients (68 5 per cent), stage III in 2 patients (10·5 per cent) and stage IV in 4 patients (21 per cent)

All anastomoses (16 single layer extramucosal and 3 two layers handsewn) were performed on patients judged haemodynamically stable by the anesthetist. In one patient we performed Dudley's wash-out, and in 7 (37 per cent) we associated an other operation to the colonic resection (3 appendicectomy, 3 cholecystectomy, 1 right ovariectomy) The mean operating time was 3 h 20 min (2 h 30 min–5 h).

Eleven patients (58 per cent) developed postoperative complications not requiring a new operation, including 3 clinical anastomotic leakages (15 8 per cent). In two cases the fistulas closed spontaneously on short course of TPN Three patients (aged 78, 88 and 90 years) treated by left colon resection died for persistent sepsis (15·8 per cent), all of them were classified in the ASA IV group Two presented preoperatively a severe cardiovascular disease associated with a severe renal failure, one of these developed a minor anastomotic leakage.

Our data suggest that resection with primary anastomosis is a valid option for experienced surgeons in the treatment of diverticular disease and colonic carcinoma complicated by localized or diffuse peritonitis, either purulent or fecal In fact the mortality rate is mainly related to the dramatic effect of sepsis on preexisting severe organic disease

A more accurate selection among the patients in the group ASA IV requiring left colon resection, focusing on the negative effect of association between severe cardiovascular and renal failure, could probably reduce the rate of anastomotic leakage, also if it does seem not to affect the necessity of reoperations for persistent or recurrent peritonitis

The value of the faecal occult blood test in the diagnostic assessment of proctological patients?

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Because a complete diagnostic assessment of the colon in proctological patients is not feasible or possible, we retrospectively tried to find out, if the test on faecal occult blood (FOBT) has any benefit to diagnose a colorectal malignancy In our office endoscopy is limited to rectosigmoidoscopy or partial colonoscopy If the history, the findings at proctological examination and limited endoscopy do not give any clue for more proximal colonic disease, a FOBT was performed. This test was also repeated after any proctological treatment From 1991 till 1994 3015 FOBT's were evaluated. Two hundred and forty-four tests of 225 patients (105 males, 120 females, average age 55 years) were positive In 130 patients (58 per cent) an ileocolonoscopy or barium enema were performed one caecal carcinoma was found. In 19 patients we advised further colonic examination, but it was not performed. In this group a woman with anaemia died, who strictly declined the colonoscopy In the other 89 patients, in which diagnostic assessment was already performed or the FOBT was positive because of diet, medicines or prior haemorrhoidal therapy, two patients died (gastric cancer and myocardial arrest) This group of patients with positive FOBT was compared with a group of patients, in which a carcinoma in the anorectum or colon was diagnosed (60 patients, 19 males, 41 females)

The results of this retrospective study show, that the diagnostic use of the FOBT has no benefit in the diagnostic assessment of proctological patients to exclude a colorectal malignancy.

Application of stapling in colorectal surgery

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Aim: Most of digestive tract surgical procedures results with a need for performing anastomosis. This study aims to summarize the results of introducing a variety of stapler types and stapling techniques in intestinal anastomosis, during large bowel and rectum operations that finished with restoration of continuity of alimentary tract.

Material and methods: In the period October 1995–December 1997, 46 surgical procedures of large bowel and rectum, that included intestinal anastomosis, were performed A group of patients consisted of 21 male and 25 female, average age 68·3 Out of above mentioned procedures 30 cases were scheduled operations (65·2 per cent), 16 were emergency operations (34 8 per cent). Main surgical indications for intestinal resections were divided in two groups: new-growth tumours – 44 procedures (95·7 per cent of total) and others – 2 procedures (4·3 per cent of total). The following staplers were used for the reconstruction of the alimentary tract: circular CEEA, linear cutter GIA and linear TA.

Results: Out of 46 intestinal anastomosis recorded, in 23 procedures CEEA staplers were used, and in 23 procedures GIA staplers were used In all cases TA staplers used for closing colotomy. Seventeen of described above operations were anterior resection. The time of surgical procedure was shorten significantly and the degree of tissues trauma was decreased The application of staplers improved the conditions of healing, due to smaller interruption of blood supply in the area of anastomosis, resulting from proper staples placement and a limited tissue squeeze. In all described procedures a total number of one case of functional stricutre after CEEA stapler usage (i e 2 2 per cent of total) was recorded

Conclusions:

1 The application of stapling enables to perform low rectal anastomosis and avoids mutilating colostomy, even in emergency operations, ensuring at the same time the oncological radicality of the surgical procedure

2. Stapling technique allows to shorten the duration of colorectal surgical procedure significantly, improves aseptic and homeostasis due to limitation of infection with intestinal contents, comparing to cases when traditional suturing technique was used

3. The use of staplers has proven to decrease the number of postoperative

complications, connected with insufficient tightness, bleeding and stricture in the anastomosis area.

L-glutamine but not short chain fatty acids attenuates the inflammation and oxidant injury in experimental colitis

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Short chain fatty acids (SCFA) and L-glutamine are metabolic fuels for colonocytes. The aim of this study was to investigate the role of L-glutamine and SCFA enemas on mucosal damage and inflammation in experimental colitis.

Methods: Colitis was induced with trinitrobenzenesulphonic acid in ethanol (TNBS-E) in rats. Saline (n=14), prednisolone (n=13), mesalazin (5-ASA) (n=14), L-glutamine (n=14) and SCFA (n=13) enemas were applied twice daily to the rats for 7 days after induction of colitis. Sham group (n=9) received only saline enemas. Rats were killed on the seventh day and their colonic macroscopic inflammatory scores (MIS) were determined. The activity of mucosal gamma glutamyl transpeptidase (GGT) and plasma, liver, colonic mucosal molondialdehyde (MDA) levels were measured. Same measurements but no enemas were done in the control group (n=7).

Results: There were significant differences in MIS between sham and colitis (P<0·001) groups. The MIS of the colitis group was higher than SCFA and glutamine groups (P<0·05). While the mucosal GGT activity was diminished in prednisolone, 5-ASA and SCFA groups when compared to the control, in colitis, sham and L-glutamine groups this enzyme activity did not change. The colonic mucosal, liver and plasma MDA levels were significantly less in the prednisolone and glutamine groups than the colitis group.

Conclusion: L-glutamine enemas decreased the severity of colitis both morphologically and biochemically. L-glutamine had also an antioxidant effect in colonic mucosa, liver and plasma.

The risk of lymph node metastases in pT1 rectal cancer

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The purpose of our study was to identify pathologic parameters of pT1 rectal cancers related to the risk of lymph node metastases (LNM). The assessment of this risk is of crucial importance to select patients eligible for local excision of rectal cancer.

Materials and methods: A total of 301 patients underwent resection for rectal cancer. In 25 cases (8·3 per cent) the tumour extended into the submucosa without invasion of the muscolaris propria (pT1). The slides from these 25 tumours were re-examined.

Statistical comparison between patients with and without LNM was performed considering the single follow variables:

- size of the tumour: diameter <30 mm vs diameter >30 mm;
- cellular differentiation: G1–2 vs G3–4;
- lymphatic vessels invasion: presence vs absence;
- high-risk histology vs low-risk histology.

Lesions with low degree of cellular differentiation (G3–4) and/or with signs of lymphatic vessels invasion were classified as having a 'high-risk histology'.

Results: LNM were found in four out of 25 tumours (16 per cent). Only one of the four tumours presenting LNM were smaller than 30 mm. In the group of the 23 well or moderately differentiated tumours (G1–2) only two showed LNM.

The size of the tumour and 'high-risk' histology were found to be statistically significative to determine the risk of LNM.

Conclusions: Our data suggest that tumours of the low and middle third of the rectum smaller than 30 mm well-differentiated and without lymphatic vessels invasion have a low risk for LNM and should be considered for local excision.

Synchronous hepatocellular carcinoma and adenocarcinoma of the rectum. Case report and review of the literature

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Introduction: Multiple tumours are particularly frequent in some types of cancer, such as colorectal, breast, head and neck carcinomas. A review of the literature indicates that the incidence of synchronous tumours of the colon and rectum ranges from 2–12·4 per cent. The incidence of synchronous extra-colonic malignancies is less well defined, but it appears to be 0·7–6·7 per cent. The reasons whereby a subgroup of patients develop more than one malignancy remain unclear and in this respect multiple tumours represent a biological challenge.

Aim: The aim of the study is to summarize the presentation, clinical investigations and treatment of a patient with synchronous hepatocellular carcinoma and adenocarcinoma of the rectum and to remind the possibility of simultaneous malignancies.

Case report: The patient was a 53-year-old man whose medical history revealed diabetes mellitus, transient ischaemic attack and alcoholic liver disease associated with mild liver cirrhosis (Child A). A routine clinical check up (physical examination, abdominal ultrasonography and later CT scan) revealed a 6 cm tumour in the VI–VII segment of the liver. The needle biopsy showed hepatocellular carcinoma. During the investigations rectal bleeding occurred, rectoscopy and colonoscopy with biopsy demonstrated an intraluminal rectal adenocarcinoma. As the first step abdomino-perineal resection was performed, histology showed $pT_2N_0M_0$ rectal adenocarcinoma. Three months later after a control check up the encapsulated liver tumour was resected. Metastases were not found, histology showed hepatocellular carcinoma. There were no intraoperative or postoperative complications.

Conclusions: The literature has highlighted the incidence of synchronous colonic neoplasms, but the risk of a second carcinoma developing at extracolonic site also must be considered in patients with colorectal tumours. Although simultaneous rectal carcinoma and hepatocellular carcinoma is extremely rare in the literature. The authors emphasize the need for detailed preoperative clinical investigations to find not only the metastases but both synchronous colonic and extracolonic malignancies.

Immunobiological approach to colon cancer staging: retrospective evaluation and prospective trials after 15 years' experience

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In spite of recent progress achieved in early diagnosis through endoscopy, and in surgical treatment with the help of new technology and in new adjuvant radio-chemotherapy protocols the colon cancer death-rate has not yet been reduced. We consider as a possible explanation of this failure the inadequacy of the present colon cancer staging criteria, that do not allow to characterize the effective biological activity of the disease and appear likewise not to coincide with the neoplasm's natural history. When we started our experiences on this topic the basic question was the folowing: is it possible to classify and to stage colon cancer not only on the grounds of its diffusion, histological type and grading, but on the grounds of its biological expression as well?

At the outset we tried to design experimental models integrating biological markers (serum and tissue CEA levels) and standard staging parameters (TNM-UICC, Duke's classification, grading) in 193 patients operated on colon cancer. In spite of the employment of several serum new biomarkers for the staging and the monitoring of colon cancer patients, serum preoperative and postoperative CEA evaluation is to date considered the most reliable test for clinical application in colon cancer. K-Ras serum pre and postoperative test is up to day under evaluation.

Retrospective and prospective evaluations about cellular 'in situ' immunological response did not show correlation with colon cancer staging.

Intranuclear DNA imaging may be to day considered as a marker of the biological behaviours of colon cancer Our results achieved on 20 patients seem to confirm the data of literature: high proliferative cellular activity and aneuploidy appear correlated only with the extent of the primary tumour ($P=0.022$) and with a severe prognosis, but by multiple full thickness sampling performed by through-cut biopsy by Silvermann-like needle we noticed that the most atypical clones were present in samples taken from the infiltrating part of the tumour, near the serosa

Reconstruction of colonic continuity following the Hartmann operation: risky surgery?

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Aim: The Hartmann operation remains indicated in both emergency and programmed surgery. In many cases the patient may be subjected to a second operation to restore colon continuity In this sense, a correct evaluation of the risk/benefit ratio is essential to decide the convenience of this second reconstruction operation

Material and methods: A review is made of the case histories of patients subjected to terminal colostomy closure after the Hartmann operation in the period 1991–1996, with an evaluation of the morbidity-mortality statistics involved

Results: A total of 23 patients (16 males and 7 females) were studied. Mean age was 54 years (range 29–73). These patients represented 25 per cent of all Hartmann operations performed in this same period. In all cases initial surgery was carried out on an emergency basis (17 due to benign pathology and 6 for tumours). The mean time elapsed between the two operations was 10 months (range 2–21) The surgical technique adopted for reconstruction was not uniform. There were posterior complications in five patients (21·7 per cent). two wound infections, one pleural effusion, one Douglas haematoma, one case of moderate faecal incontinence, one eventration, and one case of anastomatic dehiscence. Mortality was zero

Conclusion: In emergency surgery of the left colon the techniques of choice are resection with primary anastomosis and the Hartmann operation. In our series major reconstruction morbidity following Hartmann's operation was 8·7 per cent, with zero mortality. Thus, surgery for reconstructing colon, continuity does not pose excessive problems in those patients subjected to the Hartmann operation.

Local recurrence after rectal resection for cancer. Retrospective study in 154 cases (1970–1991)

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From 1970 to 1991 we performed 154 rectal resections 88 anterior resections Knight, 27 anterior resections Dixon, 33 Hartmann operations, 6 other resections (Kraske – 2, Babcock – 2, Duhamel – 1, van Hackenegg – 1). The surveying program included 114 cases The local recurrence (L R) appeared in 32 cases (28 1 per cent) From 1988 we introduced the preoperative radiotherapy in all cases and that was an important element in reducing the risk of L R the incidence of L.R. before 1988 was 29 3 per cent (28 from 77 cases); for the cases with preoperative radiotherapy the incidence of L.R. was 6 2 per cent (two from 32 cases).

The L.R. appeared in 78·1 per cent cases in the first 2 years and only in 12·5 per cent cases in the third year postoperatively. The incidence of L.R was related with the tumour stage· 0 per cent for stages A and B1; 16 7 per cent for stage B2 and 50 per cent for stage C

The position of the recurrence was· anastomotic in 9 cases (28·1 per cent), pelvic in 18 cases (56 2 per cent) and we have no position data in 5 cases (15 6 per cent) The resection of L.R was possible in 11 from 32 cases (34 4 per cent) The survival at 5 years for the cases with L R was 18·7 per cent. There was no case alive at 6 years

The influence of age on prognosis and management of patients with colorectal carcinoma

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Aim: To examine the factors affecting prognosis and management of patients younger than and older than 65 years of age with carcinoma of colon and rectum.

Materials and methods: 822 consecutive patients with colorectal cancer who had operative treatment between 1984 and 1994 were studied retrospectively. Patients were divided into two groups and compared. Group 1 included 565 patient aged less than 65 years, Group 2 comprised 257 patients aged 65 or more.

Results: There was no significant difference between the two groups with regard to the mode of presentation, the location and type of pathology, the histological grade, the incidence of curative and palliative operations, and the postoperative morbidity and mortality The obstruction and perforation was more common in in the elderly ($P<0{\cdot}0001$) Clinical relevant postoperative complications were observed in 20 per cent of patients in Group 1 and 25 per cent of patients in Group 2 ($P>0{\cdot}05$). Four per cent and 7 per cent of patients in Group 1 and 2 had an anastomotic leakage ($P>0{\cdot}05$) The postoperative mortality rate was 3·4 per cent for younger group and 6·6 per cent for older group ($P>0{\cdot}05$) Of these patients. 3·1 per cent and 20 7 per cent in Group 1 and 6 per cent and 25 per cent in Group 2 underwent elective and emergency surgery respectively ($P>0{\cdot}05$) The mortality rate was higher in those who underwent emergency surgery but was not significantly related to the age. The actuarial 5-year survival rates for older and younger patients were 33 and 45 per cent respectively ($P<0{\cdot}05$)

Conclusions: Age alone has no characteristic effect in the treatment of colorectal carcinoma.

Surgery for local recurrence of rectal carcinoma

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Introduction: Local recurrence of rectal cancer after surgical resection with curative intent occurs early, about 70–80 per cent within the first 2 years of follow-up after previous curative therapy The symptoms at presentation are different, depending on surgical treatment of primary tumour. A rigorous follow-up after resection of primary colorectal cancer including endorectal ultrasonography lead to detect early recurrence.

Aim: The aim of this study is to evaluate surgical treatment in patients with local recurrence of rectal carcinoma

Patients and methods: Between January 1992 to December 1997 10 patients underwent intention for local recurrence of rectal carcinoma after curative resection. We have analysed, previous surgery with curative intent, original stage, free interval time to recurrence, symptoms of recurrence site of recurrence, treatment, survival-time.

Results:

	Surgery	Dukes	Time to recurrence	Symptoms	Site of recurrence	Treatment	S
Case 1	AR	A	12 m	Pain	Extralumen	APR	A
Case 2	APR	B	22 m	Pain	Extralumen	Local resection	A
Case 3	AR	B	1ª–12 m	Rectal blood	Anastomosis	AR	D
			2ª–36 m	Pain	Extralumen	APR	
Case 4	APR	C	36 m	Pain	Extralumen	Local resection	D
Case 5	AR	C	14 m	Rectal blood	Anastomosis	APR	A
Case 6	AR	C	1ª–12 m	Rectal blood	Anastomosis	APR	A
			2ª–36 m	Pain	Extralumen	Local resection	
Case 7	AR	C	21 m	Rectal blood	Anastomosis	Hartman	D
Case 8	AR	C	48 m	Rectal blood	Extralumen	Palliation	D
Case 9	AR	C	6 m	Pain	Extralumen	Colostomy	D
Case 10	AR	B	12 m	Pain	Extralumen	APR palliative	A

AR. anterior resection, APR abdominoperineal resection, S. survival, D died, A· alive

Median time to recurrence was 22 months. The symptoms were anal pain and rectal blood. patients treated with AR the recurrence was at the anastosis and required an APR was performed initially, the site of recurrence was extralumen. Fifty per cent of the patients were treated with radiotherapy too.
Conclusions: In the treatment of locally recurrence colorectal cancer the approach is multidisciplinary and based on previous radiation therapy and surgical resection. The influence of early detection of local recurrence on resectability and prognosis is stated so its important to detect it in asymptomatic period.

Evaluation of neuromodulation in patients with rectal dyschezia and voiding dysfunction

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Recent results from the Marks clinic show the use of neuromodulation in treatment of both rectal dyschezia and voiding dysfunction. The aim of this study was to determine which patients with rectal dyschezia and voiding dysfunction might be suitable for treatment with neuromodulation.
Patients and methods: Twenty-seven patients were included in the study and selected for implantation of a neuroprosthesis using a urodynamic evaluation before and during subchronic stimulation. A Medtronic screener and a Flexon wire were used for neuromodulation. Four men and 20 women were included with a mean age of 33±15 years. In this group eight patients were suffering from rectal dyschezia and one patient had severe incontinence.
Results: After implantation of the neuromodulation only two patients still had complaints of dyschezia and incontinence was no longer present in these patients. Of 10 patients with spastic pelvic floor syndrome, nine responded well to the treatment. Those not responding to neuromodulation had mainly acontractile detrusors.
Conclusion: The ideal candidates for neuromodulation are those patients with a spastic pelvic floor syndrome or with an anatomical dysfunction that is not easily treated surgically.

Prognostic value of carcinoembryonic antigene (CEA) in colorectal cancers

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Introduction: It has been shown the CEA is an independent prognostic factor in colorectal cancers. In this study, the relation between preoperative CEA level and morphological and pathological features of tumour, stage, relapse and mortality were investigated.
Patients and methods: Between 1990–1997 67 patients were operated on due to colorectal cancer. There were 36 male patients and 31 female patients. The ages of patients ranged between 23 and 83 (median 56 years). The tumour was present in the right colon in 18 patients, in the left colon in 20 patients, in the rectum in 28 patients and in both right and left colon in one patient. There were 2 (3 per cent), 26 (38·8 per cent), 28 (41·8 per cent), 11 (16·4 per cent) patients in Dukes A, B, C, D stages respectively. The mean follow-up time was 35 months. The patients were divided in the two groups: (a) normal CEA level (<5 ng/ml), (b) high CEA level (>5 ng/ml). The CEA level was normal in 42 patients (62·7 per cent) and high in 25 patients (37·3 per cent). These two groups were compared concerning 20 different parameters including morphological and pathological features of tumour, relapse and mortality. Survival analysis was evaluated with the use of Kaplan Meier long rank method and other parameters were evaluated with the use of Chi-square test.
Results: When the relation between CEA levels and 20 parameters were evaluated, a relationship was determined among the tumour size, liver metastasis, tumour fixation, haemoglobin level, pathological TNM stage, relapse and mortality ($P<0{\cdot}05$). In univariate analysis, it has found that the patients with normal CEA levels survival longer than the patients with high CEA levels (69 months vs 25 months) ($P=0{\cdot}0001$).
Conclusion: This result of this study has shown that patient with high CEA level had large, fixed tumour with high incidence of liver metastasis and poor survival. Preoperative high CEA levels may be an indicator of advanced intraabdominal disease and poor outcome.

Ultra-low coloanal anastomosis for rectal carcinoma of the anorectal junction

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Aim: Traditionally, radical resection of low rectal carcinoma of the anorectal junction (tumour located at 1 cm or less from the anal ring) is abdominoperineal resection because of the necessity of both to achieve a 2 cm distal margin and to preserve anal sphincter integrity. The aim of this study was to investigate functional and oncological outcome of ultra-conservative resection for rectal carcinoma.
Methods: Among 261 patients treated for rectal carcinoma, between 1990 to 1996, 16 consecutive patients (10 males, 6 females; age 64) had conservative resection for a lesion of the anorectal junction. All the tumours involved the bowel wall at digital examination and at endorectal ultrasonography and were contraindicated for local excision. The mean distances between the tumour and the anal verge, and between the tumour and the anal ring, were respectively 3·62 cm and 0·84 cm. Rectal resection with resection of the internal sphincter was carried out, allowing a distal margin of 2 cm in all cases. An ultra-low coloanal anastomosis was performed, in association with a colonic **J** pouch in half patients. Twelve patients (75 per cent) had preoperative radiotherapy. Dukes' modified stage of the tumour was: B1=8, B2=1, C1=1, C2=4, sterilized=1, D=1.
Results: There was no postoperative mortality. Two patients had permanent colostomy for pelvic haemorrhage and anovaginal fistula. After a mean follow-up of 42 months (range 9–89), two patients died from distal metastases and there was no local recurrence. Actuarial survival was 75 per cent at 5 years. Continence (Kirwan scale) was normal for half of patients and was altered (occasional minor leak) for the other patients. Functional results were similar after partial resection of internal sphincter than after subtotal resection, but they were better after pouch than after straight anastomosis.
Conclusion: Local recurrence rate and long-term survival were not affected by conservative resection for rectal carcinoma of the anorectal junction, which can be an alternative to abdominoperineal resection for selected patients. Furthermore, our results suggest that performing a colonic pouch is most important that preservation of internal sphincter to achieve good functional results after ultra-low coloanal anastomosis.

Hereditary nonpolyposis colorectal cancer and Turcot's syndrome

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Aim: The aim of the present study is to report the case of a family with the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome in association with Turcot's syndrome.
Introduction: Turcot's syndrome denotes the syndrome of familial adenomatous polyposis (FAP) and a primary tumour of the central nervous system. Using molecular evidence Hamilton *et al.* defined two germ-line defects associated with Turcot's syndrome, one of which is usually found in FAP, and the other is usually found in HNPCC.
Material and methods: We studied families with HNPCC that included a patient with a primary brain tumour. The families were identified from the HNPCC Registry that we are performing in our hospital. HNPCC was defined according to the criteria of the International Collaborative Group.
Results: We found a family with a 16 year-old male member who developed a glioblastoma involving the right parietal area of the brain.
Discussion: Two major inherited syndromes with colorectal neoplasia can now be characterized, FAP and HNPCC. In FAP there is a germ-line alteration of the adenomatous polyposis coli (APC) gene. In HNPCC a

germ-line mutation occurs in one of a group of genes involved in DNA nucleotides mismatch repair, including *hMSH2*, *hMLH1*, *hPMS1*, *hPMS2* Molecular genetic work has found that about two-thirds of cases of Turcot's syndrome arise from mutations of APC gene, whereas one-third come from mutations of mismatch repair genes, the same genes mutated in HNPCC The central nervous system tumour are also distinctive depending on which gene is mutated, those with FAP syndrome exhibit medulloblastoma-type tumours, meanwhile HNPCC syndrome is associated with glioblastoma multiforme tumours, like our case.

Conclusions: Central nervous system tumours in HNPCC have not been well documented and require further investigation. Symptoms and signs suggesting central nervous system tumour in HNPCC families require prompt and careful investigation

Large bowel volvulus

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Intestinal destruction is a common pathology in the Kosovo an Metohija population. Although the incidence of large bowel volvulus is decreasing, cases continue to present.

From 1993 to 1997 there were 38 cases of large bowel volvulus, 23 cases were men and 18 were women. The mean age was 55 years Thirty-four patients had volvulus of the sigmoid colon and 4 had volvulus of the caecum Seven of the sigmoid and 2 of the caecal cases had gangrene.

Sixteen patients were treated with a Hartmann operation, sigmoid colectomy with primary anastomosis in 12 cases, right hemicolectomy in 2 cases and detorquation with fixation in 8 cases Postoperatively there were 6 wound infections, 2 wound dehiscence, 2 stoma complications, 1 myocardial infarction and 5 other cases of cardiorespiratory complications There were 5 deaths in this series

According to analysis of the series of our patients with large bowel volvulus, we noticed that the most important role in the appearance of volvulus is accustomed or congenital predisposition. In our series, volvulus of sigmoid colon according to older age is the result of accustomed predispositions, and the rotation is to the left

Surgical treatment of tumours of the right colon

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In this article we give our experience in operative treatment of the tumours in the right colon in last 6 years. Retrospectively analysed data were gathered from history and operative records for 61 operated patients (20 per cent of all operated carcinomas of colon and rectum). The relations of sexes was nearly equal (31·30 male:female) Almost 41 per cent (25) of operated patients were in the group of the seventh decade, and 97 per cent (59) of them were older than 50. According to localization 50 81 per cent (31) belongs to coecum, 37·71 per cent (23) to ascending colon, and 11 48 per cent (7) to hepatal flexure as well as the transverse colon Resectability was 67 21 per cent (41). Right hemicolectomy with systemic lymphadenectomy was performed in all resectabe tumours Paliative operation in 32 79 per cent (20) were performed by ileotransversostomy As postoperative complications we had 2 (3·2 per cent) fistulas, 7 (11 4 per cent) supurations and 5 (8 per cent) deshicenties of operative wound, 2 (3·2 per cent) eviscerations and 2 (3·2 per cent) cardiopulmonary complications. Postoperative mortality rate was 1·64 per cent (1). The adenocarcinoma was verificated in 59 cases (96 72 per cent). Anastomosis after resection was created as termino-terminal in 20 cases (32 78 per cent), and termino lateral in 41 cases (67 22 per cent) one row continued or single modified suture by Gambe in 40 cases (65 57 per cent), and double file suture in 21 cases (34·43 per cent). By TNM classification, in 46 cases (75 4 per cent) after radical operation was found $T_2N_1M_0$. An appropriate diagnostic studies performed in early stages of illness may lead us to early and more radical surgery that can only give us a hope in longer life expectancy

Colonic obstruction: emergency resections with anastomosis

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Choice of surgical options in the treatment of colonic obstruction is still controversial Many authors suggest one stage procedure in colon obstruction because of elimination of the distended colon as a source of postoperative morbidity and mortality and reduction of the risk of malignant disease spreading. Between 1992 and 1996 in Surgical Clinic of Niš 270 patients were surgically treated because of the colon cancer (rectum excluded). In 81 patients (30 per cent) the disease manifested as an acute obstruction. Of 81 patients, 19 patients were younger than 65 years of age (23·45 per cent) and 62 (76 55 per cent) older than 65 years of age (range 38–86). Sex ratio was 54 per cent male and 46 per cent female. In 50 (62 per cent) patients, with 'closed loop', syndrome, we have done one stage resections with primary anastomosis In cases of the right colon obstruction we have done the right hemicolectomy 66 per cent (33 patients) and for the left colon obstructions we have done the subtotal colectomy 34 per cent (17 patients) We did not perform segmental colectomy and intraoperative colonic lavage 20 patients (40 per cent) presented with one or more associated medical at the time of operation In the subgroup treated with subtotal colectomy, complications occurred in 6 of 17 patients (35 per cent) and postoperative mortality was 11·7 per cent (two patients died, one as a result of anastomotic dehiscency and stercoral peritonitis the other as a result of pulmonary embolism) In the subgroup treated with right hemicolectomy morbidity was 27·2 per cent (nine patients) and mortality was 9 per cent (three patients died. one as the result of cardiopulmonary insufficiency, second as the result of cerebral ischaemic attack and third as the result of anastomotic leakage) Our opinion is that the low postoperative morbidity and mortality in the present series justify application of one stage resection as the safe method in the treatment of many obstructive cancers of colon ('closed loop') when performed by experienced surgeons in colorectal surgery

Synchronous colo-rectal carcinoma. Diagnostic and therapeutic implications

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The reported prevalence of synchronous primary adenocarcinoma of the colon and rectum ranges from 2 to 9 per cent.

In a series of 723 patients with colo-rectal carcinoma treated consecutively from November 1973 to April 1997, seven patients (0·96 per cent) were identified to have a double carcinoma (synchronous cancers), located in separated colonic areas Patients with familiar polyposis or inflammatory bowel disease were not included in this study All patients were male and the average age was 55 4 years (range 42 to 80 years).

The cancers were located in different segments: two patients had the index carcinoma located in the caecum and the synchronous in the sigma, two others in the ascending colon and in the sigma respectively, one in the sigma and in the transverse colon, one in the rectum and in the caecum and the last in the transverse colon and in the ascending colon.

Preoperative diagnosis of synchronous lesions was achieved in only two cases. Endoscopy was performed in all patients, while air contrast barium enema studies were recorded for only two patients. In five patients the synchronous lesion was identified by palpation during laparotomy

Tumours were staged in accordance with TNM staging of colonic and rectal cancer. TNM staging of index cancer (the most malignant lesion) revealed four patients in stage II (Dukes' B classification), one patient in stage III (Dukes' C) and two patients in stage IV (Dukes' D).

In regard to extent of the resection in two patients the carcinomas were so remote that total colectomy was necessary. In other three cases we elected to employ a conservative policy, resecting each growth radically through a right hemicolectomy in conjunction with a sigmoid resection in two cases In two patients with a metastatic synchronous cancer cecostomy or ileostomy were performed

There were no hospital death and morbidity. We do believe that surgical strategy may change based on preoperative and perioperative total colonic evaluation. Second lesions must be identified because the location of synchronous tumours should infuence the extent of primary colonic resection. We agree with most authors on the need of full examination of the colon in all patients presenting with primary colorectal cancer and pancolonoscopy should be used as routine effective screening for synchronous cancers so that optimal initial treatment can be delivered. The choice of surgical proceeding is based on multiple factors, such as neoplasm's characteristics and location, the number of lesions and the grade of colonic dilation in the obstructing tumours: all patients require a more large resection and subtotal colectomy, when possible, is the gold standard treatment.

The Hartmann's operation for the treatment of colorectal diseases

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Aim: The aim of the study is to present the authors experience with Hartmann's procedure.
Material and methods: Between January 1990 and October 1997 the Hartmann's operation was performed in 58 cases. Average age of patients was 67·3 (range 37–90 years). Fifty patients were operated in case of colorectal cancer and eight because of complicated diverticular disease and others. Clinico-pathological staging (Dukes' scale) for cancer tumours was: Dukes' A – 0 cases, Dukes' B – 12 cases (28 per cent), Dukes' C – 29 cases (58 per cent), Dukes' D – 9 cases (18 per cent). Majority of patients (49 cases – 84·5 per cent) were operated on emergency in case of intestinal obstruction or/and peritonitis.
Results: Postoperative complications were observed in 36·2 per cent of patients (21 cases) mostly due to surgical wound infection (14 patients – 24·1 per cent). Four of the patients (6·8 per cent) died in the postoperative period. All patients who died were operated in emergency because of complicated colorectal cancer and they had very serious additional diseases. Mean age of patients who died was 74 years. Mean hospital stay was 17 days.

After a mean period of 140 days (60–380 days), the continuity of the gastrointestinal tract was restored in 50 per cent (4 out of 8) patients who had survived the Hartmann's procedure performed in non neoplastic diseases, and in 16 per cent (8 out of 50 cases) only of patients who had undergone surgery due to carcinoma. In 58 per cent of patients (7 out of 12) intestine was anastomosed by circular stapler. In four patients (33 per cent) decolostomy was performed laparoscopically (laparoscopically assisted). In this kind of operation can be problems with intraabdominal adhesions, liberation stoma from stomal canal and identification of the rectal stump. Mean operating time laparoscopically assisted decolostomy was 155 min, mean hospitalization time – 6·5 days. There were no postoperative complications.
Conclusions:
1. Hartmann's operation allows patients to survive a fecal peritonitis and neoplasmatic obstruction and it can be performed when the intestinal anastomosis is too risky.
2. High complication rate is connected by relatively high percentage of advanced cases.
3. Laparoscopic assisted decolostomy after Hartmann's operation looks like a save procedure and in the future it can cause increase number of patients who had decolostomy which will improve the quality of life a lot.

Pyoderma gangrenosum at the parastomal site in patients with inflammatory bowel disease

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Aim: Pyoderma gangrenosum (PG) is a rare skin disease, characterized by chronic, deep, necrotizing ulcers, usually localized at the lower extremities. In 30–40 per cent of cases, PG is associated with inflammatory bowel disease (IBD, either ulcerative colitis (UC) and Crohn's disease (CD), especially with active disease. The occurrence of PG at the parastomal site has been rarely reported.
Material and methods: Parastomal PG at the ileostomy site was observed in six female patients (5 UC and 1 CD patients; mean age 44·8 years, range 27–61 years). In three cases PG occurred from 4 to 8 weeks after total proctocolectomy, ileoanal anastomosis (IAA) and temporary diverting ileostomy for UC. Only one patient (patient 1) showed active disease (severe pouchitis, pelvic abscess and laboratory findings of inflammation). In two patients PG appeared four weeks after total colectomy and Hartmann's procedure for severe UC. In one of them proctoscopy revealed severe proctitis and laboratory findings of inflammation were present. The CD patient developed PG seven years after ileorectal resection with Hartmann's procedure for recurrent disease. No symptoms or signs of disease were present. A skin biopsy of the ulcer was obtained in three patients and was entirely compatible with PG diagnosis. Cultures of the skin lesions were positive for *E. coli* only in patient one. Oral methylprednisolone (16–40 mg/day) was administered in all patients associate to intralesional steroid injection.
Results: Complete healing of the skin lesions was obtained in two patients with inactive disease and partial healing in the CD patient. Replacement of the ileostomy was necessary in the other cases.
Conclusions: Although PG is usually described in associated with active disease it may run a course independent of intestinal disease activity and respond poor to intestinal resection. In our experience PG was associated with active disease in two out of six patients (33·3 per cent) and replacement of the ileostomy was necessary to resolve the PG. The other four patients did not show any sign of active disease. However medical therapy was unsuccessful also in two of them.

Abdominoperineal resection of the rectum for cancer: results with the Lazaro da Silva continent perineal colostomy

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Aim: To assess the technique of continent perineal colostomy described by Lazaro da Silva as a new alternative to abdominal colostomy. To prove the effectivenss of this technique and its capability to produce neoanal continence in the long term. The technique is based on hindering of the colonic transit by physically uncoupling myoelectric activity and creating circular valves in the colon, thus, it was decided to assess its reproducibility by different surgeons.
Materials and methods: Between 1994 and 1997, 16 patients with low rectal cancer underwent the procedure. The technique consists of: 1) disruption of the myenteric plexus by performing three circular seromuscular incisions in the passing down the pelvic floor sigmoid colon; 2) construction of three circular valves at the sites of seromyotomies for mechanical hindering of the stool passage, and 3) achievement of regular defecations by means of self-performed enemas through the perineal colostomy.
Results: Of the patients, 56 per cent (n=9) were Dukes' A and 44 per cent (n=7) Dukes' B with their age in the range 46–69 years (median, 59·3). There were no deaths and no tumour recurrences have occurred so far. Thirty-eight per cent of the patients (n=6) are able to defecate without enemas and in 62 per cent (n=10) enemas were absolutely necessary for achieving defecations. In all full continence for solid faeces was achieved.
Conclusions: The initial results with this technique have been encouraging. This technique proved effective in all patients thus treated and led to achievement of satisfactory neoanal continence. The Lasaro da Silva perineal colostomy is very easy to perform; results reproduced by different surgeons were similar. Because of the small number of cases larger studies are needed before its routine application in clinical practice.

Combined interventional radiological treatment of rectal tumours and their liver metastases

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Aim: To assess alternative interventional treatment results for rectal tumours and liver metastases.

Materials and methods: Sixty-one patients with inoperable lumen restricting rectal tumours were treated with the combination of selective (ADM and/or MMC + Gelaspon) chemoembolization, intraluminal cryotherapy and LDR Cs-137 irradiation. The catheter was placed into the superior rectal artery or into the hypogastric arteries. In 29 patients having liver metastases additional selective hepatic artery chemoembolization was performed in altogether 55 cycles. For response assessment rectal and abdominal US and CT examinations were carried out. Survival times and quality of life were assessed.
Results: I. Rectal tumours: acute bleedings were stopped and tumour volume was reduced in all cases. CR: 0, PR: 36, MR: 23, P: 2. II. Multiple liver metastases (*n*=29): CR: 0, PR: 13, MR: 12, P: 4.
Conclusion: Combined chemoembolization, intraluminal cryotherapy and LDR CS-137 after-loading interventional radiological treatment proved to be efficient as a palliative treatment in inoperable rectal tumours and their hepatic metastases.

Cost-benefit problems in colorectal surgery in Hungary

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The costs of surgical procedures are increasing all over the world, because of new technical instruments and high salaries of surgeons and their assistance. That is a great problem in Hungarian hospitals, because the relatively low Hungarian GDP allows less and less budget for the hospital costs. The prices of instruments are well determined, but the prices of one hour's work in the operating room is not fixed even today in Hungary.

Clinical study was performed between 1 January 1990 and 31 December 1997. The goal of this study was to compare the perioperative data of patients with elective colorectal resections because of malignancies. The operator and the preoperative preparation of patients were the same. The patients divided into two groups. One part of them had operations with colon-anastomosis, the other with rectal anastomosis.

Data of 203 patients (105 female and 98 male) were analysed. One hundred and sixteen anastomoses were performed on the colon (68 of them were hand made and 48 were made by linear staplers). The rectal operations were divided into three groups. There was a group for patients with hand made anastomoses, a group for patients with anastomoses sutured by one EEA circular stapler, and there was one group for patients operated on with double-stapler technique. The groups were comparable. Distribution of sex, mean age and mean body weights were similar.

The mortality and complication rates were similar in the groups of patients with colon anastomoses. But the operative time was significantly shorter in the group of anastomoses made by linear staplers. Unfortunately the cost of operation was higher because of prices of linear staplers. The author could not determine how much cost was spared by the shorter operating time.

The mortality rates were similar in the groups of patients with rectal anastomoses. The complication rate was the lowest and the operating time was the shortest in the double stapling group. Unfortunately the cost of operation was the highest in that group because of the prices of two staplers. The author could not determine how much cost was spared by the shorter time and the lowest complication rate.

Our experience in complex treatment of thyroid carcinoma

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Introduction: We have undertaken a retrospective review of all 19461 patients with different thyroid diseases operated in the period between 1967 and 1997. The patients were segregated into groups according to disease: 6344 nodular goitre, 11820 multinodular goitre, 1297 Grave's disease. 6091 patients with nodular goiter with clinical and paraclinical symptoms of hyperthyroidism.

Methods and procedures: Thyroid cancer was found in 867 patients of department general surgery (4·4 per cent) – 791 patients with differentiated cancer/papillary carcinoma – 642 patients follicular carcinoma – 149 patients undifferentiated cancer in 27 patients, sarcomas – 2 cases and medullary carcinoma – 45 cases. In period of 1 to 4 years after operation all of patients with undifferentiated carcinoma and sarcoma died. In cases with differentiated carcinoma 3 patients died, and with madullar carcinoma 8 died.

Results: For all of patients with carcinoma were reserved surgery treatment (thyroidectomy), and during the last 3 years we performed organ-peserveted operation in case with differentiated carcinoma-patients without regional lymph node metastases underwent lobectomy, istmectomy and contralateral subtotal resection 193 patients underwent neck lymph node dissection for metastases. These patients were not treated with radioiodine therapy. In cases with undifferentiated carcinoma we performed thyroidectomy with lymph node dissection.

Surgical treatment of secondary hyperparathyroidism in patients with kidney substitution therapy

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The aim of the present study was to evaluate the usefulness of surgical treatment in patients with secondary hyperparathyroidism.

Material and methods: Between January 1990 and July 1997, in 15 chronically dialysed patients and in three patients after renal transplant manifesting secondary hyperparathyroidism symptoms surgical treatment was performed. The diagnosis was based both on the estimation of levels of PTH, total and ionized calcium, phosphates, alcaic phosphatase in blood, and imaging procedures like ultrasonography and 99-mTc subtraction scintigraphy. The indications to surgical treatment were: obstinate ailments like generalized prurigo, bones and joints pain and muscular weakness with no amelioration after pharmacological treatment.

Results: The main procedure was subtotal parathyroidectomy in 17 cases (94·4 per cent), its extent, however, was in each case determined during surgery, depending on the quantity and size of parathyroid glands found. In all cases the immediate intraoperative histopathological examination of resected tissues was performed. In 10 (55·5 per cent) patients resection of thyroid gland tissues was carried out due to goiter, among them in 1 (5·6 per cent) case occult papillar carcinoma in manifested transient hypocalcaemia with good response to pharmacological treatment. Good results of surgical treatment reflecting in both ailment withdrawal and the normalization of PTH and phosphates in blood were obtained in 16 (89 per cent) patients. In 2 (11 per cent) patients the ailments lessened but did not disappear.

Conclusions: Surgical treatment of secondary hyperparathyroidism by subtotal parathyroidectomy is efficacious and entails a low risk of complications.

Surgical treatment of goiter in elderly patients

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Aim: The aim of the study is to underline differences in goitre surgery of elderly patients.

Material and methods: Since 1984 till 1996 there were 4122 patients operated on for goitre in III Department of Surgery. Among them 161 (3·9 per cent) were 70 or more years old, 13 (0·3 per cent) were over 80 years old. The eldest patient was 95 years old. There were 135 women and 26 men in this group (female:male ratio=5:1). Duration of goiter development varied from two months to 50 years, and in 50 per cent of cases was longer than 10 years. In 30 cases (18·6 per cent) thyroid gland weighed more than 300 g. In 61 cases (37·8 per cent) it was endothoracic or substernal goitre. In 43·5 per cent of cases it was benign nodular goitre, but in 22·4 per cent of patients there were thyroid gland neoplasms. The most common in this group was anaplastic carcinoma of thyroid (41·7 per cent), the second one was follicular carcinoma (16·7 per cent). Seven patients (4·3 per cent) died in postoperative period, all of them operated for anaplastic carcinoma of thyroid. The most common complication was unilateral paralysis of vocal cord, which occurred in 7 cases (4·3 per cent).

Conclusions:

1. Thyroid surgery in elderly age does not carry significantly higher risk than in the other age group.
2. Goitre in elderly patients is significantly more often malignant.
3. Very often goitre in this group is localized substernally or endothoracally.

Long-term survival in non-functioning malignant neuroendocrine tumour of the pancreas metastatic to the liver: case report

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Introduction: Neuroendocrine tumours of the pancreas represent less than 0·5 per cent of all pancreatic tumours. Only in 15–45 per cent of cases are they are clinically 'non-fuctioning'; of these, 80–90 per cent are malignant. We report a case of non-functioning malignant neuroendocrine tumour of the pancreas metastatic to the liver, analysing the diagnostic and therapeutic challenges that these tumours determine.

Case report: K.G., white, male, 60 years old, with a history of epigastric pain, loss of weight, previous diagnosis of unresectable neoplasm of the pancreas and palliative chemo-immunotherapy (cisplatinum, ethoposide, α-interferon). Despite this treatment, progression of both primary tumour and metastases was observed. Eight months after first diagnosis, the patient developed nausea and vomiting and was then admitted to our Department. A huge mass was palpable in the upper abdomen with no clinical evidence of an endocrine syndrome. Patient assessment included: a CT scan, which confirmed a 20 cm mass arising from the body and the tail of the pancreas with multiple liver metastases, obstruction of the splenic vein and local venous hypertension; a coeliac axis angiography showing a complete obstruction of the splenic vein; meta-iodo-benzilguanidine (MIBG) and 111-Indium-pentetreotide scintigraphies, both negative; a dimercapto-succinil-acetate (DMSA) scintigraphy which showed a huge uptake in the upper left abdomen and in the liver. Plasma levels of islet cell hormones, histamin, serotonin and 5-HIAA urinary excretion were normal. A distal pancreatectomy with splenectomy, omentectomy, regional lymph node dissection and biopsy of an hepatic lesion was performed. The postoperative course was uneventful. Pathological report and immunohistochemical studies were consistent with a neuroendocrine neoplasm of the pancreas with lymph node and hepatic metastases.

Postoperative adjuvant therapy was administered: Cisplatinum + Ethoposide, 6 cycles; 5-Fluorouracil + Folinic acid, 4 cycles; octreotide, 1 mg per day, during the entire follow-up period. The patient is alive and fit 32 months after surgery with good control of the hepatic lesions and no signs of local recurrence on serial CT and US scans.

Conclusions: Non-functioning islet cell tumours are metastatic at the time of diagnosis in 80 per cent of cases. Somatostatin receptor scintigraphy improves the localization of both the primary tumour and metastases at the same time. However, with the most applied isotopes, either iodine-123-labelled octreotide or indium-111-labelled-DTPA (diethylene triamine penta-acetic acid) octreotide (pentetreotide), a significant rate of false negatives is observed. For this reason, recent studies have underlined the use of dimercaptosuccinil acetate (DMSA) scintigraphy. Besides imaging modalities, a differential diagnosis from a ductal carcinoma of the pancreas requires accurate immunohistochemical work-up. Advanced presentation does not preclude prolonged overall survival (35–63 per cent at 5 years). Therefore, aggressive surgical therapy is recommended whenever possible and pancreatic resection remains the treatment of choice both for cure and for palliation. Adjuvant mono- or multi-drug chemotherapy schedules have been tested with dismal results, while long-acting somatostatin analogues administered postoperatively seem to inhibit tumour growth.

Thrombo-embolic prophylaxis with low molecular weight heparine at endocrine surgical patients

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Patients with endocrine surgical diseases of the adrenal gland are at high risk of thrombo-embolic complications because of obesity, cardiomyopathy, hypertension.

Of 21 patients operated for hormone active adrenal tumours thrombo-embolic prophylaxis were applied with low molecular weight (LMWH) heparine (enoxaparine, sandoparine). The diagnosis of the patients were Cushing syndrome of 9 cases, Conn syndrome of 7 cases and 5 cases of Pheochromocytoma. The type of operations were adrenalectomy in all cases. There were 18 women and 3 men, the age of the patients were 29–66 years (average 52 years). The indication of thrombo-embolic (TE) prophylaxis were varicositas of the lower extremity in 10 patients, obesity in 12 patients, cardiomyopathy at 7 cases and chronic bronchitis at 9 cases. There were 17 patients with two or more TE risk factors. The LMWH was applied 2 hours before operations once daily postoperatively for 7 days subcutaneously. The observed laboratory parameters were WBC, RBC, Hgb, Htc and platelet preoperatively and on the 5th and 7th postoperative days.

The Htc level changed from 0·41 to 0·38, the Hgb level from 14·1 to 13·8 g/l and the platelet level from 225 to 210×10^9/l. The changes of the laboratory parameters were non-significant, it was due to the operation and to the hemodilution. The side effects of the TE prophylaxis were pain at the site of the injection in two cases and mild local bleeding at the operation site in one case.

There were no thrombo-embolic complications in the perioperative period.

Our results were that LMWH is an effective preventive anticoagulant agent at high thrombo-embolic risk endocrine surgical patients.

Laparoscopic resection for pheochromocytoma: predictive factors for peroperative difficulties

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Laparoscopic approach is increasingly used for resection of adrenal lesions. We here report the difficulties we encountered during the resection of eight pheochromocytomas, in order to determine predictive factors for perioperative difficulties.

Material: Eight patients (median age 43 year: 12–70) presented with symptomatic unilateral pheochromocytoma (left/right: 4/4). All patients had complete endocrine workup, abdominal CT and MIBG scintigraphy. Preoperative phenoxybenzamine an intraoperative phentolamine plus labetalol were used for blood pressure (BP) control.

Results: All patients had their pheochromocytoma successfully removed by a transabdominal laparoscopic flank approach. The periadrenal fat was resected 'en bloc' with the adrenal lesion. Median lesion size was 4 cm (2–11 cm); median operative time 180 min (120–240); median blood loss 150 ml (20–800). Two complications occurred: one ischemia of the left kidney upper pole most likely related to clipping of an accessory upper renal artery, and bleeding in another patient having sustained, during the same laparoscopic operation, removal of a symptomatic 12 cm cyst of the kidney; bleeding was laparoscopically controlled. She was the only patient requiring blood transfusion.

Blood loss >400 ml and intraoperative hypertensive peaks (systolic BP >200 mm Hg) occurred in patients with highly secreting lesions (urinary epinephrine or norepinephrine levels 16 to 50 times above normal ranges) and in patients with lesions greater than 5 cm.

Conclusions: Laparoscopic adrenalectomy for pheochromocytoma is a safe approach but highly secreting lesions and/or with size larger than 5 cm lesions, seem to be the major factor for intraoperative haemodynamic instability and blood loss.

The dependence of surgical intervention extent on the morphological characteristics of thyroid cancer

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The purpose of this investigation has been to work out recommendations concerning the extent of surgical intervention for thyroid cancer (TC) according to its clinicomorphological characteristics. The complexes (cyto- and histological, ultramicroscopic) investigation of 105 various forms of TC was carried out prior to, during and after operation. Attention was paid to the localization and number of nodes, their dimensions, the histological form and the differentiation degree, that was appreciated by points according to three morphological attributes (the percentage of the typical tumour structures to the total area of a neoplasm; the manifestation degree of cellular and nuclear polymorphism and the mitotic activity of a neoplasm). It was determined that the minimal extent of surgical intervention (hemithyroidectomy) is warranted in cases of highly differentiated papillary, follicular and C-cell tumours, which grow in the form of a single node with dimensions from 0·1 (microcarcinomata) to 4 cm; lympho- and haematogenous metastases are usually lacking. The extirpation of both lobes and isthmus of a gland with the revision of regional lymph nodes is imperative with the tumours of the medium differentiation degree, as there were noted multicentric growth in 46 per cent of cases and bilateral lesion in 23 per cent. Histologically these TC have more frequently papillary-follicular structure or conform to the diffuse-sclerotic version of the papillary TC. 34·7 per cent of patients of this group have metastases in the regional lymph nodes. The low differentiated tumours were characterized by diffuse multicentric growth, they often grow into the thyroid capsule and surrounding tissues. Histologically they are represented by amphicrine and combined tumours, preserving the signs of the A-cell and C-cell differentiation. With these tumours numerous lympho- and haematogenous metastases can be observed. In such cases, when treated by operative surgery, it is necessary to perform the extirpation of the entire thyroid gland and the nech fatty tissue with the lymph nodes.

The surgical treatment of hyperthyroidism – a review of 129 cases

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Aim: The authors provide a review of the personal experience and literature data in order to assess the role of surgery in the treatment of selected cases of hyperthyroidism.

Materials and methods: A retrospective study was carried out on 129 patients (121 female and 8 male, ratio f:m=15:1), with an age range from 17 to 78 years (mean=46 years), who underwent surgery for diffuse (Graves' disease) or nodular thyrotoxicosis (Plummer disease).

Preoperative diagnosis was achieved by physical examination, thyroid function tests, ultrasonography, thyroid scan and fine needle aspiration biopsy.

Results: Bilateral subtotal thyroidectomy was performed on 49 patients with Graves' disease as well as for 31 cases with toxic multinodular bilateral goitre. Forty-nine patients with unilateral nodular thyrotoxicosis underwent subtotal (or total) lobectomy.

Histology, performed by the same pathologist, revealed a case of papillary microcarcinoma associated with a toxic adenoma and the same lesion in a nodular recurrence, 10 years after a thyroidectomy for Graves' disease.

Transient postoperative morbidity consisted of 12 cases (9·3 per cent) of hypocalcemia and 5 cases (3·8 per cent) of dysphonia.

The long-term follow-up revealed 16 patients (12·4 per cent) with hypothyroidism, 5 cases (4·7 per cent) of hypoparathyroidism and 2 cases (1·5 per cent) of persistent recurrent laryngeal paralysis.

Conclusions: Surgery is a good, safe and rapid method of therapy for diffuse or nodular thyrotoxicosis, allowing the most certain road to euthyroidism and fewer long-term complications than any other treatment currently available.

Clinical experience in Hurthle cell tumours

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The World Health Organization Committee for the Histological Typing of Thyroid Tumors designates Hurthle cell tumours as a variant of follicular tumours but many authors do not agree with this decision because they believe that the clinical behaviour and the prognosis of these neoplasms is dependent more on the presence of Hurthle cells than on this histologic pattern.

There is also a strikingly remarkable difference in the prognosis reported in several series. This difference probably may be explained by the difficulty to distinguish benign tumours (adenomas) from the real malignant Hurthle carcinomas.

In the period 1987/97 six patients with Hurthle cell carcinomas and four patients with Hurthle cell adenomas underwent primary surgical treatment at our Institute (8·1 per cent of all thyroid carcinomas).

The diagnosis of Hurthle cell tumour was based on the presence of more than 75 per cent Hurthle cells and the malignity on capsular or/and vascular invasion.

All the patients with Hurthle cell cancer underwent total thyroidectomy and three with Hurthle cell adenoma thyroid lobectomy, one total thyroidectomy.

Follow-up time ranged from 1 to 8 years after surgery (mean 4·5 years). There was no death and no recurrence.

We have studied the nuclear DNA content in Hurthle cell tumours: 3 adenomas were euploid and1 was aneuploid, 4 carcinomas were aneuploid and 2 were euploid.

The results in our study of the DNA content and nuclear DNA ploidy are not uniformly consistent enough to allow a distinction between benign and malignant neoplasms and to evaluate the prognosis but we must consider that the number of patients and the follow up are still too limited.

Diagnosis and treatment of differentiated thyroid carcinoma: our results

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Objectives: To evaluate the diagnosis, surgical treatment, postoperative complications and the prognosis of the differentiated thyroid cancer.

Patients and methods: We reviewed retrospectively 224 patients operated for thyroid cancer between 1977 and 1997. Two hundred and four cases (91 per cent) were thyroid differentiated carcinoma, 12 (5·3 per cent) medullary carcinoma, 7 (3·1 per cent) anaplastic cancer. We evaluated the sex, age, diagnosis procedure, surgical treatment, complications and survivals at 10 years.

Results: Median age of differentiated thyroid carcinoma 44·9 years (13–76), 102 (68 per cent) were female and 48 (32 per cent) male. The incidence of papillary carcinoma was of 178 (76·4 per cent) and, for the follicular 23 (10·2 per cent). The median age for papillary carcinoma was 44·3 years (13–76), and for follicular cancer was 45·5 years (range 29–65 years). With regards to surgical treatment, total thyroidectomy was performed in 106 patients (70·6 per cent), subtotal thyroidectomy in 52 (21·3 per cent) and lobectomy in 8 (7 per cent). The most relevant complications were: injury of the recurrent laryngeal nerve: bilaterally 2 (0·9 per cent), and 6 cases (2·9 per cent) unilaterally. Permanent hypothyroidism was observed in 12 cases (8 per cent). Ten-year survival in papillary carcinoma were 149 (83 per cent) and follicular 17 (73·9 per cent).

Conclusions: Thyroid differentiated carcinoma is significantly more frequent in females. The age is relevant with regards to the prognosis, taking into account the fact that most of the deaths produced by papillary carcinoma occur in the over 40 age group. The prognosis is also determined according to the extent of the primary tumour. In the follicular case, tumours exhibiting moderate or marked invasion had the worse 10-year survival.

Modified intra-arterial calcium stimulation with venous sampling test for preoperative localization of insulinomas

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Background: To determine the accuracy and safety of a modified intra-arterial calcium stimulation with the venous sampling test (ASVS) for preoperative localization of insulinomas. Modification included stimulation with a fixed low dose of calcium gluconate, additional stimulation in the distal splenic artery, and no insulin sampling in the left hepatic vein.

Methods: In 10 patients showing biochemical evidence of organic hyperinsulinemia, 0·45 mmol of Ca^{2+} was injected into the gastroduodenal, superior mesenteric, proper hepatic, proximal, and distal splenic arteries during angiography. Insulin levels were measured in samples taken from the right hepatic vein before 30, 60, 90, 120, 180 and 300 s after Ca^{2+} injection.

Results: Insulin gradients with an increase of more than fourfold indicated direct tumour supply, two- or fourfold correlated with collateral, and less than twofold correlated with normal tissue vascularization. ASVS localized all the adenomas of the pancreatic head (n=3) and body (n=2) and two of four adenomas of the tail correctly, as confirmed by surgery. Two adenomas of the proximal pancreatic tail were erroneously localized to the body segment, but the fault was rectified by angiography. In one patient with a negative ASVS and without exploration, the diagnosis of insulinoma was revised.

Conclusion: ASVS with a fixed low dose of calcium gluconate is a highly accurate and safe method for preoperative localization of insulinomas. Sampling in the left hepatic vein can be routinely omitted. Additional stimulation in the distal splenic artery seems helpful in surgical decision making, but additional experience is needed.

Recurrent laryngeal nerve injury after thyroid gland surgery (risk factors)

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Introduction: Since the thyroid gland has a close neighbourhood with vital organs and structures, thyroid surgery does require a special knowledge, skill and an exclusive experience. Thus, protection of recurrent laryngeal nerve during thyroidectomy operations constitutes an important part of surgery. From this point of view, we planned this study to investigate recurrent laryngeal nerve injuries and its causes after thyroid surgery, performed in our 4th Surgery Clinic.

Patients and methods: Between January 1990 and November 1996, totally 465 patients underwent thyroid surgery at this institution. From this population, patients having experienced recurrent laryngeal nerve palsy had been followed-up at least 12 months and evaluated retrospectively. The statistical analyses were assessed with Chi-square or Fischer's exact test. P-values were determined for univariate analysis. Multiple logistic regression test was peformed for multivariate model. $P<0·05$ values were accepted as significant.

Results: Male and female patient numbers were 53 (11·4 per cent) and 412 (88·6 per cent) respectively. Medigan age was 37·7 years (10–75). Totally, recurrent laryngeal nerve (RLN) palsy occurred in 12·2 per cent of patients. The permanent palsy was 2·5 per cent and the transient palsy was 9·7 per cent. According to the number of nerves at risk, the rate of RLN palsy was 1·1 per cent for subtotal lobectomy and 5·4 per cent for total lobectomy ($P<0·01$). According to the diagnosis; the permanent RLN palsy were 2·6 per cent for euthyroid goitre and 11·1 per cent for chronic lymphocytic thyroiditis respectively ($P<0·05$). In thyroid carcinoma, the permanent RLN palsy rate was 4·7 per cent ($P<0·0001$). In recurrent goitre the rate of permanent RLN palsy were 20 per cent ($P<0·05$). According to experience; the results of permanent RLN palsy in thyroidectomy operations, performed by experienced tream, was 2·6 per cent respectively. The results of less experienced team; the permanent was 2·4 per cent. According to preservation and observation of the RLN; the permanent RLN palsy rates was 1·4 per cent respectively in observed and presented nerves. In cases, which the nerve was intended to identify but could not be found, the permanent RLN palsy rates was 1·3 per cent respectively. RLN palsy was completely transient in unexplorated cases (6·6 per cent).

Conclusion: In order to decrease the rate of RLN palsies in Education Hospitals, the cases, such as total thyroidectomy, recurrent goitre, thyroid carcinoma, chronic lymphocytic thyroiditis, which have high risk of RLN palsy, are required to be operated by experienced surgeons. Residents of Surgery should be educated by experienced surgeons and the permission to resident for thyroidectomy operations should be kept for later periods of residency.

The hyperparathyroidism of transplanted parathyroid tissue

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Introduction: The total parathyroidectomy with autotransplantation of parathyroid tissue in the forearm (TPX+AT) is established as a standard treatment for four-parathyroid gland disease beside of subtotal parathyroidectomy. The literature describes a hyperparathyroidism of transplanted tissue up to 30 per cent. This study investigates the patients with TPX+AT in the period 1982–1997.

Methods: After TPX+AT periodically the calcium blood concentration was determined; in cases of hypercalcemia the parathyroid hormone was measured. If hyperparathyroidism was detected, an ultrasonic diagnostic, occasionally a MIBI-scintigraphy was carried out. The indications for reoperation were identical to the first surgical treatment. Depending on pathological findings the parathyroid tissue was reduced in regional or general anaesthesia in several steps or only enlarged tissue was selectively removed. In some difficult cases the tissue was removed completely and cryoconservated tissue was retransplanted in cases of hypoparathyroidism after some weeks.

Results: From January 1982 to December 1997 a surgical treatment was carried out to 1882 patients (range: 8–90 years) with hyperparathyroidism. Eight hundred and three patients had a four-parathyroid gland disease (primary HPT (pHPT): n=334, renal secondary HPT (rsHPT): n=469). To 530 patients we practised a TPX+AT. In 6·0 per cent (n=29) a hyperparathyroidism of transplanted tissue occurred in the mean after 32 months (range: 3–168). In these cases and in 11 cases treated before in other hospitals we reduced the transplanted tissue, sometimes in several steps till reaching normocalcaemia. In two patients we detected after removing the parathyroid tissue at the forearm a fifth parathyroid gland at the neck or in the mediastinum. In three cases the transplanted tissue was enlarged as well as we found a fifth parathyroid gland at the neck. There were no complications of surgical treatment. The histology of the reduced tissue demonstrated in 17 per cent (n=5) a diffuse and in 83 per cent (n=24) a nodular hyperplasia of the transplanted parathyroid tissue.

Conclusion: The TPX+AT is a sufficient treatment of the four-parathyroid gland disease. In 1·8 per cent (n=6) of pHPT and in 4·9 per cent (n=23) of rsHPT a hyperfunction of the transplanted parathyroid tissue occurred. The treatment was without problems and without complications. There were no cases of malign degeneration of transplanted tissue.

Solitary metastasis of renal clear cell carcinoma in a follicular thyroid adenoma: case report and review of literature

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Introduction: Metastases of renal cell carcinoma (RCC) to the thyroid presenting as a clinically palpable nodule are uncommon and may cause clinical and pathological diagnostical difficulties. They can appear years after the primary RCC was resected or before the RCC has been detected; as they usually appear as a solitary 'cold' nodule in I-131 scans and may be confused with primary thyroid tumours.

Case: A 79-year-old white man presented a 5×4 cm solitary hetero-echogenic, partially intrathoracic nodule in the right thyroid lobe. Its size was not reduced after 6 months of TSH suppressive treatment. FNA showed follicular proliferation. He had a past history of radical left nephrectomy for a RCC 3 years earlier ($pT_2N_0M_0G_2$, clear cell subtype). No evidence of recurrence had been detected in his follow-up. A right thyroid lobectomy and isthmectomy were performed; an intraoperative frozen section study was negative for malignancy. The definitive histological report was: metastasis of clear cell renal carcinoma inside a follicular adenoma, there was focal infiltration of the capsule and another 2 mm foci of metastatic RCC cells was found in normal thyroid parenchyma; thyroglobulin immunohistochemical reactivity was present in the adenoma and normal follicle cells, and was absent in the clear tumoural cells. One year after lobectomy the patient remains well, without evidence of further dissemination of the RCC.

Discussion: The most common metastatic tumour to masquerade as a primary thyroid tumour is renal cell carcinoma. In our case FNA and frozen section failed in the identification of metastatic RCC. Cytological diagnosis of thyroid RCC metastasis has been reported: cytomorphology is complemented with cytochemical fat staining. Histological differential diagnosis is with primary thyroid tumours with clear cell features; characteristic of metastatic RCC are: multifocality, optically clear cytoplasm, sinusoidal vessels, and large amount of cytoplasmic glycogen and fat. Thyroglobulin immunohistochemical staining is useful but diffusion of this marker from entrapped follicles may result in absorption by RCC cells. Autopsy studies in general oncological cases report a 10 per cent incidence of metastatic thyroid disease. Melanoma and breast tumours are the most frequent causes (40 per cent and 21 per cent), but most of the clinically detectable thyroid metastases come from renal tumours. Many of the reported cases occurred in abnormal thyroids; alterations in blood flow in nodular thyroid has been related to that observation.

The prognostic significance of thyroid metastasis of RCC vary according to the different cases in the literature: survival ranging from 32 months to seven years after surgical exeresis, prognosis thus not appear to be as poor as for thyroid metastasis from other primaries. If the metastasis is solitary resection can be curative.

Conclusion: Solitary RCC metastasis must be considered in the differential diagnosis of a thyroid nodule, even when several years have passed after a nephrectomy for this kind of tumour. A correct diagnosis may lead to a curative surgical procedure.

Insular (poorly differentiated) thyroid carcinoma: report of two cases and review of the literature

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Insular thyroid carcinoma (ITC) is a rare form of poorly differentiated thyroid carcinomas (TC) arising from follicular cells occupying morphologically and behaviourally a place between the well differentiated and anaplastic TCs. Although arguable, ITC is viewed nosologically by WHO as a variant of follicular TC. ITC usually occurs in an older group than well differentiated TC, and it is an aggressive and often lethal tumour. Its incidence in the USA is very rare; more cases have been described in Italy and in Paraguay (about 70 cases reported in the literature). Proper diagnosis of ITC is specially relevant because its prognostic meaning.

Cases: Two cases of ITC were found among 63 cases of TC treated in our centre in a nine year period. *Case 1:* A 53-year-old white woman presented with a 5×4 cm hard, fixed solid nodule in the left thyroid lobe, the nodule was 'cold' in the isotopic scan, FNA showed follicular proliferation. Marked infiltration of the strap muscles by a hard tumour was appreciated in the surgical procedure. Frozen section confirmed malignancy and a total thyroidectomy was performed. Definitive histological diagnosis was: ITC. I-131 remnant ablation was undertaken one month after surgery (200 mCi). Local cervical recurrence and bone and lung metastases that concentrated I-131 were present 5 months after thyroidectomy. A cervical debulking procedure and tracheostomy was performed. Severe hemoptysis, and widespread metastatic dissemination caused death seven months after diagnosis. *Case 2:* A 46-year-old white woman presented with a 6 cm solid lobulated, rapidly growing, hard nodule in the left thyroid lobe. 'Cold' in the isotopic scan, FNA showed follicular proliferation. The histology of the left lobe disclosed the diagnosis of ITC. A total thyroidectomy was completed as a second procedure. I-131 ablation of remnants was undergone (100 mCi). Four years after thyroidectomy a serum thyroglobulin rose strikingly and a 4×5 cm solid mass appeared in the right pterygopalatine fossa; the ascending ramus of the right mandible was partially destroyed. I-131 scan showed a pathological uptake in the right pterygopalatine area, no lung or other bone deposits were shown. FNA was diagnostic for metastasis of a poorly differentiated TC. Two separated doses of 200 mCi of I-131 therapy have resulted in a complete remission.
Discussion: The diagnosis is based in microscopic features: presence of round or oval nests composed of small uniform tumour cells. The growth pattern is predominantly solid, but microfollicles containing colloid may appear. Mitoses are always present. Necrosis is frequent, as well as capsular and vessel invasion. There is immunohistochemical reactivity for keratin and thyroglobulin; not for calcitonin. Cytological diagnosis is difficult; the main cytological features of ITC are: high cellularity, necrotic background, low grade of atypia, nests, and cytoplasmic vacuoles. The insular pattern may result in misdiagnosis of medullary carcinoma and other neuroendocrine neoplasms. It may be also confused with anaplastic TC when the growth pattern is solid throughout.

Because its follicular origin, ITC may concentrate I-131, a feature useful for diagnostic and therapeutical purposes.

Prognosis of ITC is poor: in the largest series 60 per cent of the cases apparently cured by surgery developed recurrences, and about 50 per cent died because this tumour.
Conclusion: Radical surgical treatment of TC is indicated when an histological pattern of ITC is found in the surgical specimen. Its propensity for local recurrence and early distant metastases demands an exhaustive follow-up.

Fine needle aspiration biopsy in the evaluation of thyroid nodules

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The purpose of this study was to investigate the confidence of fine needle aspiration biopsy (FNAB) in the preoperative diagnosis of benign and malignant thyroid nodules.

FNAB cytology results were compared with histopathologic results of 57 patients with thyroid nodules whom were operated in the Department of Surgery, Manisa Celal Bayar University, Faculty of Medicine between January 1997 and December 1997.

The rate of inadequate specimens was 5·3 per cent. Five aspiration biopsies were positive for malignancy, and the diagnosis was confirmed histopathologically in two of them. Thus, there were three false positive cytology (5·6 per cent). Two of four patients with proven carcinoma had benign cytological diagnosis, a false negative of 3·7 per cent. The sensitivity, the specificity, the positive predictive value, the negative predictive value and the diagnostic accuracy of this method were determined as 50, 94, 40, 94, 90·7 per cent, respectively.

As a conclusion, FNAB can be used as an initial diagnostic method in the evaluation of thyroid nodules, but since the sensitivity and the positive predictive value are low, it is not suitable to decide the cancellation of the operation according to only benign FNAB results without using other diagnostic procedures.

Surgical treatment of suprarenal gland tumours: analysis of our own clinical experience

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The aim of the study was the analysis of 127 patients operated on because of suprarenal gland hypertrophy and tumours in our Department during the period 1959–1994. The majority of the patients – [103 (81·1 per cent)] had been treated for hormonally active diseases. The remaiing 24 (12·9 per cent) for non-active tumours and most of them have been incidentally diagnosed. Amongst patients with hormonally active tumours 46 (36·22 per cent) suffered from pheochromocytoma, 14 (11·02 per cent) patients from Conn's syndrome, 5 (3·93 per cent) from virilizing tumours and 38 have had Cushing's syndrome or Cushing's disease. There were 27 operations for Cushing's disease performed in the 1960s and early 1970s.

Diagnosis and localization of adrenal gland lesions was based on clinical symptoms, hormonal studies, classical radiological investigations and recently using ultrasound and computer tomography.

The majority of the patients were operated on through the anterior transabdominal approach but now we prefer an approach through the twelfth bed of the rib.

Early results of surgical treatment of patients with adrenal gland tumours were good; late results were dependent on the histological type of the lesions.

Nodular goitre and thyroid carcinoma in children and adolescents in a moderate endemic goiter area (Lower Silesia)

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The territory of Lower Silesia is still a region of moderate endemic goitre. It is known, that in iodine deficiency areas nodular goitre and thyroid cancer is frequently common. An epidemiologic survey on iodine deficiency goitre was carried out in Lower Silesia as a part of the Polish national programme in 1992–1993 and demonstrate high goitre incidence in the population of school children in the age group 7–12 years (29·1 per cent, in 0·7 per cent a nodular goitre). The urinary concentration of iodine was low in all the investigated children (56±38 mg/l). The aim of our present investigation was to ascertain the percentage of malignancy in nodular goiter in the observed in our clinic patients from the Lower Silesia region.
Methods: The examination included 56 children (12 boys and 44 girls) with nodular goitre treated in our clinic in the last 10 years (from January 1987 to December 1997), most of them after 1991. Age at diagnosis ranged from 7 to 18 years with a mean age of 14·5 years and male/female ratio of 1:3·7. In all the patients following investigations were performed: TSH, T_3, T_4, thyroid ultrasonography, fine needle aspiration biopsy and Tc_{99} scintigraphy of the thyroid. Most of the patients were euthyroid, two children demonstrated pressure symptoms. All the patients were transferred to the Clinic of Surgery for children, where an operation was undertaken. After the operation a substitution with L-thyroxine was applied.
Results: A nodular goiter was observed especially in the elder group (11–18 years), with a dominance of girls in comparison with boys (3·7:1). Thyroid nodules were observed mostly bilateral. Thyroid cancer was observed in seven children (12·5 per cent), mostly in a single nodule. The histological examination revealed following: in 29 children colloid goitre, in 3 children cystic-nodular goitre, in 15 – follicular adenoma, in 2 – fetal adenoma, in 6 – papillary carcinoma, in 1 – follicular carcinoma.
Conclusion: Our analysis shows that there has been a striking increase in the frequency of nodular goitres in the last 10 years, with a significant percentage of malignancy (12·5 per cent), mostly in a single nodule.

Evaluation of reconstructions performed in radical operations of the tumours of Vater's papilla

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Aim: One hundred and fifty-seven patients were operated on because of pancreatic head and periampullary tumours between 1 January 1992 and 31 December 1997. The authors evaluate the results of operations of 20 tumours of Vater's papilla. All of the patients had icterus preoperatively.
Material and methods: In the diagnostic phase abdominal ultrasound, CT and ERCP examinations were performed. In 13 cases pylorus preserving pancreato-duodenectomy were undertaken: nine cases of pancreato-gastrostomy, four cases of pancreatico-jejunostomy. There was one case of the Whipple type pancreato-duodenectomy. In six cases different palliative operations were performed.
Results: During the resection of the papilla of Vater it may occur that the soft, glandular pancreas does not hold the stitches. In these cases the anastomosis insufficiency is more threatening, which was detected in two cases in the group of pylorus preserving pancreato-duodenectomy.
Conclusions: The authors in the above mentioned cases use a special operative method: the distance between the anastomosis of the pancreatico-jejunostomy and the duodeno-jejunostomy is longer, that makes possible to execute a much safer drainage in cases of potential anastomosis insufficiency.

Antioxidant deficiencies in chronic pancreatitis

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Background: Recent evidence has suggested that certain nutritional deficiencies, notably that of selenium, may play a role in the pathogenesis of pancreatitis.
Methods: Nutritional profiles were obtained from patients presenting with recurrent acute and chronic pancreatitis. Assessment included evaluation of serum albumin, calcium, phosphate, carotenoids, trace metals (copper, zinc, selenium), vitamins A and E and fatty acids. For each variable comparison was made with age and sex-matched controls.
Results: There was no significant difference between controls and patients with acute pancreatitis for any of the parameters assessed. Patients with chronic pancreatitis had evidence of nutritional deficiencies compared with controls (results shown in table). Values expressed are mean ± standard error.

	Controls (n=19)	Acute pancreatitis (n=12)	Chronic pancreatitis (n=12)
Age in years	56±19	50±11	48±11
Beta-carotene (μmol/l)	0·39±0·35	0·26±0·11	0·11±0·08*
Lycopene (μmol/l)	0·41±0·3	0·2±0·1	0·07±0·04*
Selenium (μmol/l)	0·76±0·13	0·72±0·27	0·41±0·15*

*P<0·05 chronic pancreatitis vs controls (one-way ANOVA)

Conclusions: Nutritional deficiencies affecting known antioxidants were identified in patients with chronic pancreatitis. Similar observations were not found for patients with recurrent acute pancreatitis.

Early endoscopic sphincterotomy and late elective cholecystectomy for acute biliary pancreatitis

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Biliary pancreatitis is initiated by obstruction of the ampulla of Vater by migratory gallstones. Conservative treatment is successful in 60–70 per cent of the patients. However, biliary sepsis and other complications develop in the other patients, and mortality ranges from 15 to 50 per cent. The benefit of early endoscopic papillotomy was investigated in a series of 40 patients admitted and treated in our institution for acute pancreatitis. The diagnosis of biliary acute pancreatitis was done by means of HIDA biliscintigraphy, sonography, and CT scan and standard laboratory examinations. Of the 40 patients, 34 were of biliary origin while six were alcoholic. According to Ranson's Criteria 24 patients had mild and 16 a severe acute pancreatitis.

ERCP made within 48 hours from admission in all patients showed only GB stones in four patients, CBD stones in 11, GB+CBD stones in 16, no evidence of stones but a swollen papilla with signs of inflammation in three patients. Late elective cholecystectomy was performed in all patients between 15 and 34 days after endoscopic papillotomy. Complications occurred in four patients (10 per cent) after ERCP and in three patients (7·5 per cent) after cholecystectomy. In conclusion, from the results of our study, it seems that early endoscopic sphincterotomy and late elective cholecystectomy are safe and effective in the treatment of acute pancreatitis of biliary origin.

Diagnosis and treatment of cystic neoplasms of pancreas: our results

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Aim: To evaluate our experience in managing cystic neoplasms of pancreas.
Material and methods: Retrospective review of 21 patients with cystic neoplasms of pancreas treated between 1979–1996. Clinical, histological, and treatment parameters were examined.
Results: Mean age 57 years (range 32–79), 15 females (71·4 per cent), and six males (28·5 per cent). The main clinical features were: abdominal and back pain: 13 (61·9 per cent); weight loss: eight (38 per cent); and palpable mass: five (23·8 per cent). In order of histological finding: serous cistadenomas: 11 (52·3 per cent); cistadenocarcinomas: six (28·6 per cent); and mucinous cystadenomas: four (19 per cent). Surgical treatment was performed for all patients; curative resection in 17 (80·9 per cent); and paliative procedure in four (19 per cent).
Conclusions: The preoperative determination of histological type of pancreatic cyst is very difficult. The surgical treatment is still the main form to manage this type of tumour. The survival for cystadenocarcinoma is still very poor.

The role of multivariate tumour marker analysis in the differential diagnosis of pancreatic carcinoma and chronic pancreatitis

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Aim: Differential diagnosis between pancreatic cancer and chronic pancreatitis is a great clinical dilemma in numerous cases. Pancreatic cancer is one of the most aggressive gastrointestinal malignancy. An early and exact clinical diagnosis can improve the outcome of the management of patients suffering from pancreatic carcinoma. Specific tumour markers for pancreatic cancer could play an important role in clinical screening.
Material and methods: CA 19–9, CA 72–4, CEA, TPA and AFP tumour markers were analysed with RIA technique in 162 cases (108 chronic pancreatitis, 33 pancreatic cancer, 21 cases of uncertain diagnosis). According to clinical symptoms and radiological examinations differential diagnosis could not be maintained between pancreatic cancer and chronic pancreatitis in 21 cases. Tumour marker levels were compared with intraoperative findings and with histopathological analysis.
Results: Combined multivariate tumour marker analysis detected significant increase in 13 of the 21 uncertain cases, while intraoperative fine

needle biopsy diagnosed pancreatic cancer only in 10 cases. In cases of chronic pancreatitis tumour markers were in normal range in 95 per cent (*n*=103). In cases of known pancreatic cancer tumour markers were significantly elevated in 90 per cent (*n*=30).
Conclusions: According to our results we can conclude that combined multivariate tumour marker analysis could become an important screening method in cases of uncertain differential diagnosis between pancreatic cancer and chronic pancreatitis. Preoperative knowledge of tumour marker levels can help to avoid operative mismanagement.

Analysis of mortality in acute hemorrhagico-necrotizing pancreatitis

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Despite the introduction of new drugs, changes in operation methods as well as constant advances in intensive care mortality in acute haemorrhagic necrotizing pancreatitis (AHNP) is still very high. In the years 1980–1997 there were 161 patients operated on for AHNP. Most of these patients were operated on between 3 and 72 hours after admission because of symptoms of acute severe peritonitis. In the years 1980–1989 laparatomy, cholecystectomy and choledochostomy on a T-tube extended by peritoneal lavage and drainage was performed. From 1989 the repeated laparotomy and permanent lavage were introduced in our operative treatment. In all patients blocking of gastric and pancreatic secretion, parenteral nutritional support and antibiotic prophylaxis were applied. In our patients total mortality caused by AHNP is 49 per cent (79 patients). We observed the group of eight patients (10·13 per cent) died despite of early operation (laparotomy and lavage, or repeated laparotomy) and despite very intensive treatment. Median time of treatment of early death patients was 6 days. The second group of patients (71–89·87 per cent) died between 8 and 71 days, median time of treatment was 29·2 days. All those patients died because of developed multiple organ failure and sepsis. The first insufficient organ was the lung and the second kidneys. Median time of treatment of survived patients was 74·3 days and ranged from 24 to 129 days. On the basis of our material we observe decreasing of mortality from 62·1 per cent (46 patients) in the years 1980–1989 to 37·8 per cent (33 patients) in the years 1990–1997. In our experience early operation and application of repeated laparotomy and permanent lavage allowed decrease in mortality from 62·1 per cent to 37·8 per cent.

Is gastric tonometry a good monitoring method in acute pancreatitis?

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Aim: To acquire information about the splanchnic perfusion by the use of gastric tonometry in the early phase of acute pancreatitis (AP).
Background: Gastric tonometry is an accepted method to follow changes of tissue microcirculation and tissue oxygenation in the splanchnic region. Blood extravasation, diarrhoea, and paralytic ileus all lead to hypovalaemia and shock during the early phase of AP. Also splanchnic blood flow reduction caused by hypovolaemia is disproportionately higher than it is in other regions.
Method: Patients suffering from AP were monitored by gastric tonometry for three days starting immediately at the beginning of their hospitalizations. Routinely used laboratory, and cardiorespiratory parameters were also investigated. The patients received standard treatment in the intensive care unit.
Results: More than 48 hours long intramucosal acidosis ($pHi<7{\cdot}35$) and elevated local mucosal pCO_2 ($pCO_2>55$ Hgmm) occurred in the patients only who developed necrosis of the pancreas, or multiple organ dysfunction syndrome (MODS).
Conclusions: Our initial data show the presence of long-term splanchnic bed hypoxia at the beginning of severe pancreatitis. Integrity of the gut mucosal barrier is compromised by the ischaemia, which is consequence of hypovolaemia and shock. Injured gut mucosa is of fundamental importance in the pathogenesis of MODS which is one of the most severe complications of AP. Splanchnic bed circulation monitoring may play a role in the prognosis and therapy of AP, but further investigations are needed with this method.

Evaluation of the surgical methods of pancreatic head and periampullary tumours

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Aim: The surgical treatment of the tumours of the head of the pancreas and of the periampullary tumours are the same, nevertheless the pathological behaviour of the two groups of tumours are different. The aim of this retrospective study was the comparison of operative outcome, nutritional recovery and survival of patients who underwent standard Whipple pancreatoduodenectomy (WP), pylorus-preserving pancreatoduodenectomy (PPPD) and palliative therapy of these tumours.
Material and methods: In the period from January 1992 to 1998 we observed 131 patients with tumour located in the head of pancreas and 26 patients with periampullary tumours. These included 20 tumours originated from the ampulla of Vater and six from the distal common bile duct. Symptomatic pancreas tumours are diagnosed by ERCP, transabdominal ultrasonography and computer tomography. Facultative angiography, video-laparoscopy in combination with sonography and peritoneal lavage are providing important information about the spreading of the tumour to archive satisfactory palliation endoscopically or surgically. Tumour markers such as CEA, CA 19–9 and CA 125 were also studied.
Results: The operability rate was 35 (26 per cent) in pancreatic head tumours and 18 (69 per cent) in periampullary tumours. Considering 53 resections: 11 Whipple type operation, 35 cases PPPD and seven local excisions for tumour of ampulla the mortality rate was three (6 per cent). We found that elevated serum level of CA 19–9 is the most sensitive marker of all of the tumour markers of the malignant pancreatic tumours. After non-resectional treatment seven (7 per cent) patients died in the postoperative period. After resection postoperative complications were in 12 patients (22 per cent). Delayed gastric emptying was more common in the PPPD group resulting in longer hospitalization. In PPPD group there was a better nutritional recovery and also the increase of both body weight and serum albumin level. There was no other significant difference between the survival of WP and PPPD group, but we found much better survival in patients with periampullary tumour.
Conclusions: Improved surgical techniques and improved perioperative management together decrease the surgical risk. Our data provided many evidences about the advantage of PPPD in the patients with malignant periampullary and pancreas head tumours. There is not any difference between the survival rates of WP and PPPD but the long term results and quality of life much better after PPPD.

Surgical treatment of pancreatic pseudocysts associated with chronic pancreatitis

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Chronic pancreatitis (CP) is a progressive degenerative inflammatory disease. The primary therapy in CP is symptomatic, but the intrapancreatic, intraductal morphological alterations may require non-operative interventions or surgery. Authors analysed retrospectively data of 1060 patients undergoing 1305 operations for pancreatic pseudocysts complicating CP between 1987–1996.

Results	Total drainage	Total resection	Primary resection	Subsequent resection
No.	1167 (84%)	148 (16%)	90 (61%)	58 (39%)
Preop.diab.mell	141 (12%)	37 (25%)	22 (24%)	15 (26%)
Preop. Icterus mech.	227 (19%)	21 (14%)	11 (12%)	10 (17%)
Pancreatectomy		16 (11%)	8 (9%)	8 (14%)
Head resection		46 (31%)	19 (21%)	27 (46%)
Distal resection		75 (51%)	52 (58%)	23 (40%)
Enucleation		11 (7%)	11 (12%)	0
Morbidity	78 (6·7%)	21 (14·2%)	13 (14·4%)	8 (13·8%)
Reoperation	30 (2·6%)	13 (8·8%)	7 (7·8%)	6 (10·3%)
/died/	/6+/	/3+/	/1+/	/2+/
Mortality	10 (1·03%)	6 (4·05%)	3 (3·33%)	3 (5·17%)
Hospitalization	7 days	10 days	8 days	12 days

Conclusions: The non-resective surgical procedures (ductal decompression, pseudocyst drainage) have good effect in the early period of CP. Pancreatic head resection is recommended in compression syndrome caused by the inflammatory mass. Total pancreatectomy is seldom indicated, only in cases of complete destruction of the gland. The early postoperative morbidity and mortality was not significantly higher after subsequent resections, although most of them were head resections.

Contrast-enhanced computed tomography as a prognostic indicator of sepsis in necrotizing pancreatitis

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In acute pancreatitis sepsis is very common and in necrotizing pancreatitis (NP) it develops in up to 60 per cent. It is possible to distinguish two types of sepsis in NP: one progresses slowly and appears two or three weeks after the primary pancreatitis has subsided, the other occurs simultaneously with the initial onset of pancreatitis. In the first type of sepsis, it is very important to predict the onset of this complication before the appearance of its clinical signs. In fact if a patient survives the first clinical stage, infection is the predominant cause of death in the late stage. The purpose of the present study is to evaluate to what extent it is possible to predict the onset of septic complications by means of contrast-enhanced computed tomography. We have investigated 20 patients with NP where the CT documented a necrosis. In 10 patients the extent of necrosis was less than 50 per cent of the whole gland and in 10 the extension was more than 50 per cent. In the first group the sepsis developed in one patient, in the second group in nine patients. The CT was always performed 2–3 days after the onset of the clinical signs of pancreatitis, while the signs of severe sepsis appeared 2–3 weeks after the clinical and laboratory signs of pancreatitis had subsided. In these patients we had always the surgical assessment of an abscess interesting more than 50 per cent of the pancreatic gland. All these patients underwent necrosectomy, drainage and continuous lavage. There were five deaths. We believe that when an enhanced CT shows an extent of pancreatic necrosis more than 50 per cent it is almost sure that a sepsis will develop.

Pancreatic mucinous ductal ectasia

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A 40-year-old female was admitted to our emergency department with the diagnosis of non-biliary acute pancreatitis.

The serum calcium and the serum lipids were normal and the patient denied the ingestion of alcohol or any kind of medication.

The posterior imagiologic studies included abdominal ultrasound (US) and computed tomography (CT) revealed a dilation of the entire pancreatic duct, more accentuated in the distal half of the gland. The endoscopic retrogade cholangiopancreatography (ERCP) showed a normal biliary tract without stones and the attempts to cannulate the pancreatic duct were unsuccessful. The serum CA 19-9 was normal.

The patient was explored surgically and we found a very dilated distal pancreatic duct, filled with mucin, and documented it by intra-operative pancreatography. A distal pancreatectomy was done but as the frozen section analysis of the pancreatic duct margin showed a mucinous cystadenoma we completed the pancreatectomy – total pancreatectomy with preservation of the pylorus.

The final pathologic analysis of the specimen revealed a mucinous cystadenocarcinoma (T_1N_0), a mucinous cystadenoma and hyperplasia and dysplasia along the entire duct. Two papillae: one for the biliary tract and one for the pancreatic duct.

After one year of the operation the patient has no clinical or image evidence of the tumour.

ERCP induced acute necrotizing pancreatitis

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Aim: Evaluation of the surgical treatment in complications after ERCP diagnostic procedure.

Material and methods: In the years 1994–1997, 10 patients (nine female, one male) (41–75 years old) were treated in our department for acute necrotizing pancreatitis (ANP) and cholangitis as a complication of ERCP. Indications for ERCP were bile duct stones six cases, jaundice – two, tumour of papilla Vateri – one, dilatation of common bile duct – one. Surgical treatment was indicated in patients whose clinical state was getting worse and acute necrotizing pancreatitis was confirmed. Time period between ERCP and initial surgical treatment ranged from two to 14 days (average 4·7). All patients were treated by laparoscopy according to Bradley's method. This procedure was repeated from one to 16 times (average 7·6). Total mortality rate was 30 per cent (three patients) due to multiorgan failure. The most common complications were jejunal and colic fistulas two cases, hydrothorax, respiratory and renal insufficiency. Hospitalization lasted from 27 to 180 days. Two patients developed diabetes.

Conclusions: ANP is a rare complication after ERCP but because of very heavy course and the high mortality rate it should be considered while qualifying patients for this test. Open drainage and monitoring in intensive care unit are the treatment of choice in such cases.

Unusual type of encephalopathy in the course of severe haemorrhagic-necroticans form of acute pancreatitis

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The aim of this study is the presentation of a 38-year-old woman with severe haemorrhagic-necroticans acute pancreatitis (SHNAP), who developed multiple organ dysfunction syndrome (MODS) and also had encephalopathy expressing as a flaccid paralysis of all extremities. The diagnosis was confirmed by the 10-fold rise of amylase activity in serum and urine and by the USG examination in which the extensive haemorrhagic-necroticans changes were founded in the pancreas. Also it showed the stones in the gallbladder. On the fifth day after the admission she was operated because of the increasing peritonitis and the development of MDOS. On the sixth day after the operation rapidly worsening of the clinical state of the patient was observed. The logical contact with her was impossible to obtain and flaccid paralysis of all extremities was observed. Neurological examination confirmed diffuse injury of the brain cortex as well as the brain stem. However, in performed computed tomography no changes in the brain were found. Seven days later the improvement of the clinical state was observed. The slight movement of the extremities were presented but the muscle tonus was still low without any pathological reflexes. The passive and active rehabilitation of extremities from the 14th day was applied. The extremities movement returned on the 82nd day after the beginning of the complication. She left the department after 128 days of hospitalization in good general condition and full activity.

In the recent years the introduction of antibiotics and various methods of aggressive treatment of the systemic effects of sepsis have allowed the patients to either recover or survive for a much longer period and gave enough time for the neurological complications to appear and be recognized. Since encephalopathy may occur early in the course of pancreatitis and sepsis, without direct infection of the brain and without consistent neurological changes, a reversible 'metabolic' mechanism is likely to be responsible for it. Also cytokines may directly affect the brain function. These substances cause capillary leakage, increase procoagulant activity and have direct effects on the tissue metabolism. Very important are also the changes within the lipids of the brain which are responsible for these kinds of complications. False neuromediators and neurotransmitters are another possibility.

Acute pancreatitis with hyperlipaemia and hyperglycaemia induced by alcohol abuse

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We have presented a case of acute pancreatitis with hyperlipaemia and hyperglycaemia induced by massive intake of alcohol.
Material and methods: Seven men with diabetes were admitted to our clinic during emergency duty as an acute abdomen after massive alcohol intake. Samples of blood were drawn immediately after admission. One of the signs of hypovolaemic shock presented with low arterial pressure under 80 mmHg and weak and rapid pulse rate to 150 per minute. In all, on the basis of clinical, biochemical, ultrasonography and computed tomography examinations diagnosis of haemorrhagic-necroticans acute pancreatitis (HNAP) was established. In all patients developed life-threatening complications as a multiple dysfunction organ syndrome (MDOS).
Results: Clinical and biochemical characteristics of patients with acute pancreatitis:

Age (years)	Sex	Cause	S-Amylase (IU/l)	U-Amylase	WBC (G/l)	Glucose (mmol/l)	TGL (umol/l)	Insuline (ulU/ml)
37	M	Alcohol	280	622	12·8	41·0	7090	4·13
43	M	Alcohol	2269	47563	23·5	31·9	9010	5·87
36	M	Alcohol	11820	53835	14·2	15·8	4890	4·99
39	M	Alcohol	9800	23785	17·5	13·9	4230	3·85
36	M	Alcohol	11345	48766	14·9	12·8	3980	4·15
34	M	Alcohol	7655	23985	13·9	14·8	16440	5·16
32	M	Alcohol	3356	11825	14·7	15·9	3760	3·89

It seems that hyperlipaemia is regarded as a consequence of pancreatitis, but the development mechanism of hyperlipaemia due to acute pancreatitis has not been elucidated. In the development of diabetes mellitus, with excessive intake of alcohol as an evoking factor, triglycerides remarkably increase to present a state of diabetic lipaemia. Most commonly increase triglicerydes is in serum patients with Gram-negative sepsis. This situation is in severe HNAP. In this pathological state lipoprotein lipase activity decreases due to insulin insufficiency giving an increase of triglycerides in the blood. Alcohol decreases activity of lipoprotein lipase too. It may be a consequence of impaired clearance of triglycerides from serum. It is likely that hypertriglyceridaemia predisposed these patients to develop pancreatitis, alcohol being the precipitating factor.

Tumour necrosis factor alpha in the serum of patients with acute pancreatitis

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This study was designed to examine whether the occurrence of an increased TNFα level in the serum was associated with two major clinical forms of acute pancreatitis (AP): oedematous and haemorrhagic-necrotizing.
Material and methods: For analysis 33 patients with AP were included. Diagnosis was based on the typical clinical presentation confirmed by ultrasonography, CT and an increased amylase in the serum and/or urine. For analysis patients were divided into two groups: A – with oedematous form of AP (22 patients) and B – with severe haemorrhagic-necrotizing type complicated by multiorgan failure (11 patients). Both groups received typical conservative treatment. Nine patients from the group B were operated on during first 2 weeks of hospitalization, five of them have died. On autopsy extensive necrosis of pancreas and the retroperitoneal space was seen. Blood was taken for analysis on admission and during the next three days. TNFα concentration was determined by ELISA (TNFα-EASIA, Medgenix, Fleurus, Belgium). Results were expressed as a mean ± SD (pg/ml) and the statistical differences between the groups were assessed by a non-parametric Cohran–Cox test.
Results: Measureable low values of TNFα (mean 28 pg/ml) were recorded in the serum of patients with oedematous AP (group A) and they remained essentially unchanged during follow-up. In contrast, significantly elevated TNFα (mean 491±312 pg/ml) was observed in patients with haemorrhagic-necrotizing AP (group B). It decreased only slightly during the observation period. The difference in the TNFα level between the groups was statistically significant ($P<0{\cdot}05$).
Conclusion: Serum TNFα levels are significantly elevated in patients with haemorrhagic-necrotizing, but not oedematous, form of AP and we wish to suggest that TNFα may be an important factor in the pathophysiology of this disease. The strategies aiming at the inhibition of TNFα production (e.g. pentoxifylline) or at its neutralization (e.g. anti-TNFα antibodies, TNFα binding proteins) may have a therapeutic value in the treatment of the severe form of AP.

Pancreatic exocrine function after acute biliary pancreatitis

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Introduction: According to the Cambridge and Marseilles Symposia, functional recovery of the pancreas occurs after an episode of acute pancreatitis if the primary cause and complications of the disease have been eliminated. However, recent research has shown contradictory results, owing to the difference in diagnostic methods and the proportion of patients studied in relation to the etiologic factor and severity of the disease, as well as the differences in the test utilized. Subsequent studies show contradictory results.
Material and methods: Sixty-three consecutive patients with acute biliary pancreatitis were studied. Seventeen were men (27 per cent) and 46 women (73 per cent), with an average age of 62·3 years. Forty-five were minor cases and 18 severe. All subjects underwent cholecystectomy. During the acute phase, severity was evaluated following the Atlanta criteria as well as the existence of necrosis and its percentage by means of dynamic CT. During follow-up, pancreatic exocrine function was assessed one month and six months after the AP by means of Fluorescein Dilataurate (FDL). Chymotrypsin and Fat in faeces Tests; at one year after AP the Secretine-Pancreozimine Test (PSP) was carried out. The possible existence of pancreatic exocrine insufficiency following the biliary origin AP, as well as whether this possible deficit was related to the severity of the episode, was investigated.
Results: The study showed that our patients presented no deficiency in pancreatic exocrine function at one month, six months and one year after acute biliary pancreatitis. The statistical analyses carried out in order to assess the relationship between severity of the AP and the various pancreatic exocrine function tests demonstrated that there were no significant differences.

TEST Direct T-PSP	Mild (n=45)	Severe (n=18)	TEST Indirect T	SEVERITY Mild (n=45)		Severe (n=18)	
				1 month	6 months	1 month	6 months
Bicarbonate (mEq/1)	95·5±10·7	98±15·9	FDL	60·7±27·3	58·9±20·6	53·8±24·4	60·3±24·4
Chymotripsin (KU/60')	26·4±8·7	33·6±13·9	Chymotrypsin	10·4±5·9	12·8±7·7	13·3±8·4	12·3±6·8
Lipase (KU/60')	273·5±84·7	316±186·4	Fat in faeces	3·3±2·6	3·4±2·4	2·6±2·3	2·9±1·8

Conclusions: After the primary cause of the disease has been eliminated, pancreatic exocrine function reverts to normalcy following an episode of acute biliary origin, with no relationship between functional exocrine reserve and severity of the disease being observed.

Prophylactic of the purulent-septic complications on severe acute pancreatitis

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The purulent-septic complications are one of the most important causes of death in patients with the severe acute pancreatitis. During 1990–1997, 73 patients with severe pancreatitis were treated Secondary pancreatic infection most likely occurs on 7–14 days after the onset of the disease Biochemical, immunological investigation was performed in all patients The fine-needle aspiration by ultrasonographic control was used for the detection of infected pancreatic necrosis. The aspirates analysed immediately by Gram stain, or taken for further analysis by culture The infected pancreonecrosis were observed in 29·4 per cent of patients The microorganisms causing pancreatic infection were shown to be common the enteric bacteria (*E coli* – 35 per cent, *Proteus* – 8 per cent, *Enterobacter* – 7 per cent, *Bacteroides* – 6 per cent and anaerobic flora – 6 per cent) These data pointed on that the some pancreatic infection in severe pancreatitis caused by translocated bacteria from the gut Development of the purulent-septic complications accompanied by the decrease of cortisol blood level (67·3 per cent of patients), the T-lymphocyte suppressors activity and the separation of cells in the immune response The increase of C3d level was detected in cases of purulent-septic complications Activation of the complement system cascade leads to the formation C3a, C4a and C5a anaphylatoxines, which increases the vascular permeability, stimulates the secretion of histamine from the must cells and basophils Macrophages stimulate the secretion of cytokines, such as TNF, IL-1, which create the additional effects of complement activation. The imipenem and ciprofloxacin were used for the systemic antibiotic prophylaxis These antibiotics had the most optimal pharmokinetics and antimicrobal spectrum for use in pancreatic infection The quick restoration of intestinal integrity (enteral nutrition, motility, biliopancreatic secretion) was another direction of prevention of bacterial translocation and, as the result, development of purulent-septic complications The administration of metoclopramid and prostaglandin E_2, with intestinal lavage was used for restoring of intestinal motility Applying of the pentoxyphilline and corticosteroids diminished the negative effects of cytokines. This management gave possibility decrease the number of pancreatic infections (17·6 vs 41·1 per cent of controls)

Possibility in diagnosis of pancreatic cancer

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Aim: Evaluation of diagnostic procedures in pancreatic cancer
Material and methods: In the years 1994–1997, 100 patients, aged 36–91 (mean 63), with pancreatic cancer have been treated The most common symptoms were pain in the epigastric region (68 per cent), gastrointestinal disturbances (90 per cent), body weight loss (75 per cent), diabetes mellitus (37 per cent), jaundice (56 per cent), palpable mass (73 per cent) Period from the first symptoms until proper diagnosis was: one week – 1·5 years, and was shortest in the group of icteric patients Diagnosis procedures were carried out according to adequate protocol, which comprised of the following: standard and endocavital ultrasound, ERCP, CT and coeliacography. The most effective diagnosis method were CT and ERCP (90 and 84 per cent respectively) According to the UICC/TNM scale 45 patients were classified as stage I, 20 – II, 19 – III, 16 – IV. Intraoperative histopathological examination of wedge tumour biopsy and regional lymph nodes were carried out. When no cancer was found, multiple, thick needle biopsies (after first – 35, second – 8, third – 5) In two cases of negative intraoperative biopsy, cancer cell were found during regular histopathological examination
Conclusions: The majority of patients with pancreatic cancer are diagnosed too late to perform adequate treatment Our results suggest that CT, ERCP and needle biopsy are most effective in pancreatic tumour diagnosis

Pancreatic adenocarcinoma: a review of 85 cases

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Aim: To evaluate the results of the surgical treatment of the carcinoma of the pancreas
Material and methods: We have operated on 85 patients of pancreatic adenocarcinoma during the period from January 1986 to December 1996. The location has been in the head in 79 per cent of the patients. The ag was between 28 and 85 years, with a 63·9 years average The 67·8 pe cent of the cases are included between the 60–80 years The treatment ha been surgical in all the patients, performing laparatomy in 10 cases (11· per cent); palliative surgery in 65 cases (76·5 per cent) and resectiv surgery in 10 cases (11·8 per cent), consisted of total duodenopancreatec tomy five cases and Whipple duodenopancreatectomy five. The palliativ surgery more frequent has been the choledochochoduodenostomy in 3 patients and the hepaticojejunostomy in 10 patients
Results: The operating mortality has been of 21·2 per cent (18 cases) Postoperative complications we have noticed in the 38·8 per cent (3 cases) being the most frequent the renal failure (four cases), the anasto motic leak (four cases), hepatic failure (six cases) and wound infection i seven patients The average length of stay has been of 17·6 days Th global survival rate has been of 15·8 months Concerning the technique, i the laparotomy the survival has been of 8·6 months, in the palliativ surgery of 16·3 and in the resective surgery of 21·2 months.
Conclusions: Poor improvement of the results in spite of the diagnost and therapeutics advances, earlier diagnosis should be sought The treat ment is always surgical The survival rate is around 18 months.

Oxidative stress dependent protein modification as a new signal for accelerated proteolysis in acute pancreatitis

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Growing evidence points to free radical involvement in the pathogenes of acute pancreatitis (AP) This study aimed to investigate the protei peroxidation process in cerulein induced AP Eighteen rats were divide into three equal groups: in group 1 rats acted as controls, in group 2 an 3 rats had two intraperitoneal injections of cerulein 40 ug/kg for subse quent 3 or 6 h of induction period respectively Protein carbonyls whic reflect peroxidative damage was found to increase after 3 h, 2·53±0·4 vs 1·05±0·17 in control group and return to control level 0·95±0·04 afte 6 h These data suggest that during acute pancreatitis free radicals ma play an essential role in protein damage Decrease in protein carbonyl content after 6 h suggest an elevated proteolysis of oxidatively damage proteins.

Complete traumatic transection of pancreas

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Blunt pancreatic injuries are relatively uncommon, especially complet transection.

In our department eight patients underwent surgery for blunt pancreati trauma in 1997. The aim of this article is to study two cases of complet transection of neck (1) and head (1) of the pancreas.

The patient, male 31 years old, was admitted 3 days after the assaul complaining with severe pain in the abdomen. Peritonism was clear o admission The second patient, male 26 years old, was referred to ou hospital neurosurgical department 2 days after the assault from th regional hospital with traumatic cerebral coma (Glasgow 5) Compute tomography revealed the contusion of brain Diagnostic peritoneal lavag revealed blood in abdominal cavity Both patients underwent surgery hours after admission. At laparatomy retroperitoneal haematoma and packing haematoma in lesser sac was found. We mobilized the duodenum and entered the lesser sac. The complete transection of the head on the first case and the neck of pancreas in the second case was found. Acute traumatic pancreatitis was clear with peripancreatic infiltration in both cases. No more abdominal injuries were found. Distal pancreatectomy with splenectomy in the first case and without splenectomy in the second case was performed.

Only 10 per cent of pancreas was left in the first and 20 per cent in the second case. The first patient developed pancreaticocutaneous fistula, which closed spontaneously. He was discharged home on day 32 after the surgery without diabetes, but developed exocrine insufficiency.

The second patient died on the fourth day after the surgery because of the multiple organ failure and cerebral injury.

In conclusion, survival of patients sustaining blunt pancreatic trauma correlates with associated injuries, early recognition of lesion and choice of treatment.

Hepatic growth factor (HGF): a new marker for prognosing severity in acute pancreatitis

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Aim: Serum hepatic growth factor (HGF) levels are elevated in patients with acute and chronic liver disease. Production and release of HGF may be seen in liver and other organ failure, because it is a potent and generic tropic factor. We designed this study in order to analyse the predictive value of HGF in Acute Pancreatitis (AP).

Material and methods: During 1997 we performed a prospective trial in 20 patients with certified AP of any aetiology. Severity was determined with an Original Index and Apache II. Pancreatic complications were detected by dynamic CT Scan. Serum levels of HGF were determined at admission and every day before surgery in normal patients and, in patients with AP, an enzyme-linked immune assay.

Results: Serum levels of HGF in five control patients was 0·46±0·17 pg/ml. The mean value of serum HGF in the first day, in 18 patients with AP was 1·81±0·82 pg/ml ($P<0{\cdot}005$). In two patients with AP serum levels of HGF was 0·25 and 0·61 pg/ml, and minor values to 0·70 pg/ml were considered false negative (sensitivity was 90 per cent). In patients with severe AP ($n=3$) serum HGF levels were significantly higher 6·73±1·23 pg/ml ($P<0{\cdot}005$). Finally, serum HGF level decreased progressively during the first days of treatment, except in those patients who developed pancreatic complications.

Conclusion: We demonstrate that those serum HGF levels are elevated in patients with AP; they are also significantly higher in severe cases and in cases with local complications. Those preliminary results suggest that serum HGF levels may reflect the severity and prognosis in acute pancreatitis and that HGF may play a major role in the mechanism of tissue repair.

Microscopic bile examination (Meltzer-Lyon's test) in patients with idiopathic acute pancreatitis

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Introduction: Gallstones and alcohol abuse are the most important causes of acute and relapsing pancreatitis. In about 20 to 40 per cent of cases of acute pancreatitis, no cause can be found, and these are labelled idiopathic. The presence of microcalculi in the bile juice has been described as a cause of some pancreatitis initially called as 'idiopathic'.

Background: We present a microscopic study of bilis obtained by biliary drainage in patients who were admitted on various occasions for acute pancreatitis, in whom the etiology could not be clarified.

Patients and methods: During a period of two years, bile samples of patients with acute idiopathic pancreatitis were obtained approximately after two months of having suffered the pancreatitis episode. The technique used was based on Meltzer-Lyon's modified test. Findings obtained in the microscopic study were: liquid crystals of phospholipid-cholesterol, solid crystals of cholesterol monohidrate, granules of calcium bilirrubinate and microspherulites. Moreover, we show our results obtained after a cholecystectomy.

Results: During a period of 2 years, we studied 20 patients with acute pancreatitis who were treated in our Service of Surgery. There were 14 (70 per cent) women and six (30 per cent) men aged between 33 and 72 years old. We found cholesterol crystals in eight cases (40 per cent), calcium bilirrubinate granules were obtained in 10 patients (50 per cent), and two tests were negative. Sixteen patients (all with positive Meltzer-Lyon's tests) were operated, and a standard laparoscopic cholecistectomy was performed in all. The following results were obtained: microscopic colelithiasis in five, acute colecystitis in two, cholesterolosis in seven and without pathological findings in two patients. Two patients with cholesterol crystals were treated with acid ursodeoxicholic and one developed lithiasis macroscopic with biliary colics, therefore they were cholecystectomysed. After cholecystectomy no patient presented a new episode of pancreatitis. In the group with negative tests, one patient developed lithiasis by ECO and the other one is asymptomatic.

Conclusion: Microscopic examination of the bile juice is a risk-free technique that should be included in the study of the etiology of idiopathic pancreatitis, allowing an adequate treatment of these patients and decreasing their risk of new episodes of acute pancreatitis. Laparoscopic cholecystectomy is the surgical treatment of choice.

Necrotizing pancreatitis – progress and outcome according to a well established treatment protocol

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Aim: Severe pancreatitis still remains a challenge to surgeons. At present no universal guidelines as to the best treatment options exist. Therefore it was decided to study the progress and outcomes of the disease according to a well-established treatment protocol applied among a group of consecutive patients admitted to a single institution.

Material and methods: Between 1975 and 1997, 143 patients with severe necrotizing pancreatitis were investigated and treated at our institution. A universal operative policy was chosen consisting of open packing of the lesser sac combined with continuous postoperative sac lavage at a rate of 250 ml/hour and re-explorations on demand. At re-explorations, only obviously necrotic tissue was debrided and following this, continuous lavage was started again. It was stopped in the absence of progression of necrosis and the wound was left to granulate. Gastrointestinal complications were managed by resection and ostomy; and bleeding by packing and repeat explorations.

Results: The incidence of infection was 57·3 per cent ($n=82$). Of all, 32·2 per cent ($n=46$) developed gastrointestinal necroses with resulting fistula formation; 43·4 per cent ($n=62$) – other complications caused by pancreatic ductal disruptions and related sequelae. Infection and necrosis but not the surgical technique itself were found to determine the increased risk of complications. The mortality rate was directly related to the extent of necrosis, the total number of complications, and the presence of risk factors such as advanced age and chronic comorbid diseases.

Conclusions: Abdominal complications are common in necrotizing pancreatitis, especially when infection supervenes. They require a high index of suspicion, rapid diagnosis and prompt surgical intervention together with vigorous resuscitation both performed according to a well-established protocol.

Breast

Does the type of incision of the axillary node dissection influence in the frequency of postoperative seroma?

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Aim: The seroma is the most frequent complication after axillary lymphadenectomy for breast cancer. When conservative treatment is used, the operation can be carried out by the same incision used for the resection of the mammary tumour or for an independent incision. The objective of our study was to evaluate if the fact that the incision is made in an independent way has influence in the frequency of axillary seroma.

Material and methods: We carried out a prospective study in which 109 patients operated consecutively of breast cancer were included. In 29 a mastectomy was carried out and they were excluded of the study. Of the remaining 54 the resection was carried out by means of two separate wounds and in 26 for the same wound. The number of dissected lymph nodes, days of drainage and frequency of axillary seroma in both groups were picked up. To compare the number of ganglion and the days of permanency of the drainage we employed a U-test of Mann–Whitney and to compare the seroma frequency a χ^2-square test.

Results: The data are exposed in the table. Seroma were significantly more frequent with a separate wound. No statistical differences were found for the other variables.

	Separate wound	Single wound
Seroma (%)	67	38*
Days drainage	6 (1–29)	4·6 (1–15)
Linfatic nodes dissected	18 (9–39)	18 (10–41)

*Statistically significant differences.

Conclusions: Axillary lymph node dissection through a separate incision increases the likelihood of seroma formation.

Lymphocyte subgroups in breast cancer and the effect of tumour removal

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Aim: Tumour behaviour is different among breast cancer patients. Though some prognostic factors have been defined, the cause of this difference is not clear. Alterations in host immune response to the tumour is a possible explanation. It is well known that some level of immune dysfunction exists in cancer patients. However, the effect of tumour removal on host immune function is not clear.

Material and methods: Fifty-one breast cancer patients who underwent modified radical mastectomy were studied. There were 12 patients with stage I, 16 with stage IIA, 13 with stage IIB and 10 with stage IIIA. The control group consisted of 20 women who underwent either thyroid surgery for benign causes or open cholecystectomy. Preoperative and postoperative (on the seventh day) blood samples were taken from the study and control group patients for flow-cytometric analysis. T lymphocyte, B lymphocyte, natural killer cell, T-helper, T-cytotoxic-suppressor, T active cell counts and T helper/T suppressor ratios were evaluated.

Results: T-cytotoxic-suppressor cells of the breast cancer patients were significantly higher than the control group ($P<0\cdot05$). Among the breast cancer patients T-helper cells were higher in early stages ($P<0\cdot05$). There was no differences between pre and postoperative lymphocyte profile in the control group. However, operation causes certain changes in the breast cancer patients. Postoperatively, B lymphocyte, T lymphocyte, T helper counts and T helper/T suppressor ratios increased ($P<0\cdot05$ for each). T-cytotoxic-suppressor ($P<0\cdot01$) and natural killer cell ($P<0\cdot05$) counts decreased.

Conclusions: The difference between the immune profiles of the breast cancer and the control group showed that antigenic stimulus of the tumour influences the parameters of the host immune functions. Operation had no effect in the control group, but had a certain effect in the breast cancer patients. Thus we believe that the removal of the tumour causes a considerable difference in immune parameters.

Axillary nodal clearance using minimal invasive techniques: axilloscopy: initial results

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Introduction: Axillary dissection is considered essential to provide prognostic information, and effective in obtaining local control of breast cancer. On the other hand, axillary nodal clearance is controversial because of its morbidity.

Aim: To improve postoperative comfort and decrease complications such as wound pain or lower mobility of the shoulder. We have developed a new approach using a laparoscopic technique.

Material and methods: The first step is an incision in the fifth intercostal space (10 mm, mid-axillary line), blunt dissection and introduction of a balloon rod similar to that used for the extraperitoneal herniorrhaphy. Its insufflation induces a cavity to allow the insertion of a Hason trocar for insufflation (CO_2, 6 mm pressure) and introduction of the camera; a 5-mm and a 10-mm trocar are then placed for the regular laparoscopic instrumentation (scissors, endoclips and graspers). Dissection is carried out from the Latissimus Dorsi muscle till the thoracodorsal vessels are found and singled out, removing the axillary fat towards the chest wall, and releasing the axillary vein in all its trajectory. Subsequently, dissection is followed from Serratus Lateralis muscle until the Long Thoracic nerve is found; extraction of the axillary fat through the incision of Hason's trocar. The last step is the individualized dissection of level III preserving the Pectoralis Minor muscle, and extraction of the obtained fat by the 10 mm trocar.

Results: Seventeen patients have been enrolled in our initial experience. We did not have any conversion to open procedure. The thoraco-dorsal and long thoracic nerves and the innervation of the pectoralis major muscle were dissected and preserved. The number of axillary lymph nodes obtained were more than 13 in all cases.

Conclusions: Compared to open approach, the first results show that abduction, elevation and rotary movements of the shoulder are greater with the minimally invasive technique; arm circumference is lightly increased in open surgery. However, no significant differences have been observed. The postoperative comfort and cosmetic results have been excellent.

Factors affecting disease free interval in breast carcinoma

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Aim: The duration of disease free survival following mastectomy is a matter of concern in the patients with breast carcinoma. It is a fact that some patients develop distant metastasis soon after mastectomy whereas the others have long disease free intervals. The purpose of this study was to determine the factors that affected the length of disease free interval in the patients with breast carcinoma.

Material and methods: Between 1992 and 1997, 72 patients with breast carcinoma underwent radical or modified radical mastectomy. Twenty-four of these patients developed distant metastasis following a disease-free interval of 2 to 53 months. The patients with distant metastasis were divided into two groups, based on the length of disease free interval: a) ≤16 months (14 patients); b) >16 months (10 patients). The comparability of the groups was assessed in terms of histopathological factors,

number of full-time pregnancies, age at first full-time pregnancy, body mass index (weight in kilograms divided by height in metres squared) and age. Mann–Whitney U-test and χ^2-test were used for statistical evaluation. $P<0.05$ was considered significant.
Results: There were no significant differences among the groups in terms of skin involvement, pectoralis major fascia involvement, nipple involvement, blood vessel extension, intralymphatic extension and tumour stage. However, the patients with short disease-free interval were significantly younger than the patients with long disease-free interval (≤40 years vs >40 years $P<0.05$) and more likely to have axillary tissue involvement ($P<0.05$), large tumours (2–5 cm vs >5 cm, $P=0.01$), more metastatic lymph nodes (1–3 lymph nodes vs ≥4 lymph nodes, $P<0.01$), and low parity (para <3 vs para ≥4, $P=0.01$). No significant difference was found between the groups concerning the length of survival time following the diagnosis of distant metastasis (mean 6·3 months vs 6·6 months, $P>0.05$).
Conclusion: The results of this study have shown that the patients with young age, axillary adipose tissue involvement, large tumour, increased number of metastatic lymph nodes and low parity developed distant metastasis earlier than the patients without these characteristics.

Surgical treatment of breast tumours

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Between October 1994 and November 1997 a continuous series of 115 patients (six men) with benign and malignant breast tumours was analysed. Breast cancer was found in 47 patients (one male). All the patients were included in an oncological and surgical protocol including initial evaluation and, if necessary, preoperative treatment (17 patients). Routine biopsy was made in all the breast tumours, the extent of resection according to the clinical stage of the tumour. Benign tumours were treated by lumpectomy or subcutaneous mastectomy. In breast cancers of stage I-II (29 patients), lumpectomy associated with axillary dissection were performed in 21 patients, while Madden mastectomy and axillary dissection in eight patients. In stage III (15 patients), lympectomy and axillary dissection were performed in three patients, the others benefitted from mastectomy and axillary dissection. Palliative mastectomy was made in stage IV (three patients).

Paraffin biopsy and axilliary lymph node status determined the oncologic protocol (radio-chemotherapy) in 40 patients who underwent surgery for cancer, seven patients were lost from follow-up; four patients deceased (three extensive metastasis and one stroke). The present study is limited in time.

Consequently, in advanced stages, conservative surgery can be performed, while in advanced ones oncological and surgical protcol must be extended.

Axillary adipose tissue involvement: a poor prognostic factor for breast carcinoma

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Aim: The course of the breast carcinoma is still unpredictable today. Prognostic factors may help predict the patients for aggressive adjuvant therapies.
Material and methods: Between 1992 and 1997, 72 patients underwent radical or modified radical mastectomy for breast carcinoma and were followed up on for five years (range 2–60 months). The effect of age, menopausal status, blood vessel extension, intralymphatic extension, tumour necrosis, skin involvement, nipple involvement, involvement of pectoralis major fascia, axillary adipose tissue involvement, pathologic nodal status, number of involved lymph nodes, tumour size, T (tumour) category of AJCC-TNM staging and stage on survival were studied. Survival curves were calculated using the Kaplan–Meier method. Multivariate analysis was performed using the Cox's regression model.
Results: Of the 72 patients, five had stage I, 36 had stage II and 31 had stage III carcinoma. Forty-seven (65·3 per cent) patients were found to have axillary lymph node involvement: ten had 1–3 and 37 had ≥4 positive axillary lymph nodes. Thirteen patients died of their disease between 6–25 months after their operation. Of these patients, five (33 per cent) had axillary adipose tissue involvement. There was no death among the patients with stage I disease and one death (4 per cent) among the patients without lymph node involvement. Eleven patients are still alive with distant metastasis of the malignant disease. Of these patients, four (36 per cent) had axillary adipose tissue involvement. Seven characteristics were found to have a statistically significant prognostic effect by univariate analysis: (a) age; (b) axillary adipose tissue involvement; (c) tumour size; (d) T category of AJCC-TNM staging; (e) lymph node involvement; (f) number of involved lymph nodes; and (g) stage. When these seven characteristics were assessed by Cox's modelling, stage ($P<0.01$), number of involved lymph nodes ($P=0.01$), and axillary adipose tissue involvement ($P<0.05$) were independently related to survival.
Conclusion: The present analysis demonstrates that stage, number of involved lymph nodes and axillary adipose tissue involvement independently affected overall survival so that patients with advanced stage, ≥4 positive axillary lymph nodes and axillary adipose tissue involvement had a poor survival.

A clinicopathological study of a rare clinical entity mimicking breast carcinoma: idiopathic granulomatous mastitis

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Aim: Idiopathic granulomatous mastitis (IGM) is a rare chronic inflammatory lesion of the breast clinically simulating carcinoma. The purpose of this report is to review the clinicopathological features of this clinical entity in a series of 13 cases diagnosed in our institute.
Material and methods: The notes of the patients and the slides of the biopsy specimens of 13 cases with IGM were reviewed. Special stains for organisms and immunohistochemistry for T and B markers using the primary antibody was done. The diagnosis of IGM was made according to the criteria of Kessler and Wolloch.
Results: All but two patients were of reproductive age and all were parous. The main clinical finding was the unilateral, firm, discrete mass. All patients underwent excisional biopsy and recurrence was seen in three patients. In two of these patients who had recurrences, prolactin level was high and re-excision with antiprolactinemic therapy was performed. The third patient was treated by re-excision and oral prednisone. There was granulomatous inflammation, centred on breast lobules in all patients. T-cell domination was observed.
Conclusions: Exclusion of the other causes of granulomatous lesion is necessary to make the diagnosis of IGM. The treatment of choice is unclear. Because of clinical impression of a possible malignancy, surgical excision of the lesion is necessary. In patients with delayed wound healing or recurrence after excisional biopsy, or those patients who have had an incisional biopsy only, if prolactin level is normal, re-excision and oral prednisone usage will be curative. On the other hand, patients with high prolactin level who have recurrences, medical treatment to control prolactin level must be added.

Indications for different mammaplasty techniques

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Over the last years a variety of new techniques of mammaplasty have been developed. Especially the techniques that brought a reduction of scars have readily been accepted and are routinely in use by now, like the short horizontal scar technique (Marchac) and the vertical scar techniques (Lassus, Lejour). Apart from a reduction of scars, these new techniques also were to bring better functional results, especially regarding perfusion, sensibility, motoric innervation of the nipple and the ability to breastfeed. This certainly enhanced the reliability and safety of the operation.

The attitude towards mammaplasty has changed, as some years ago most surgeons used only one or two techniques of the whole spectrum to perform all mammaplasties, irrespective of anatomical findings or the planned extent of reduction. Now, there is a variety of different methods of mammaplasty available which all have their specific indication and limitations. Thus, different indications need to be defined.

The periareolar mammaplasty is useful only for a very small reduction or a mastopexy. It is mainly reserved for a mere change of shape.

The techniques with vertical scar can presently be regarded as the standard method for resections amounting up to 800–1000 g per side, depending on the skin quality.

The techniques with L-, Z- or short horizontal scar may be used for planned resection volumes around 800–1000 g per side, which cannot be treated aesthetically by vertical scar techniques.

Inverted T-scar techniques remain the standard procedures for resections of more than 800–1000 g per side.

The definite choice of an operating method has to be made individually, considering anatomic findings as well as the planned size and shape of the breast. With further standardization, choosing the best technique for an individual patient will become simpler and clearer for the surgeon.

Using Sappey's anatomy for identifying sentinel lymph nodes in breast cancer

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The most important prognostic factor of breast cancer is an adequate staging of the axillary lymph nodes, which influences both adjuvant and surgical therapy. Morton has successfully adapted the method that he had originally developed for identifying 'sentinel' lymph nodes in melanomas to the purposes of examining axillary lymph nodes in patients with breast cancer. Using this procedure he has also made staging simpler and more accurate. Due to the close relation between the plexus areolaris, the plexus subareolaris and the plexus periareolaris, the special lymphatic system of the breast makes it possible for the vital stain to be injected under the skin of the areola rather than round the tumour itself.

The axillary lymph drainage of 85 randomly selected patients with breast cancer was studied.

Of them, 55 patients underwent direct breast lymphography. For visualizing lymph vessels Patent blue dye was injected intracutaneously into the area of the areola. The lymph vessels and lymph nodes outlined on radiographic pictures after Lipijodol Ultrafluid was injected into a prepared collector lymph vessel. The dissection of axillary lymph nodes was started by preparing the lymph nodes that stained blue. The results were evaluated in a five-year follow-up examination.

In 30 patients sentinel lymph nodes were identified by comparing results yielded by the two methods. Patent blue was injected intracutaneously into the region of the areola, then, after the exposure of the axilla and the isolation of the blue-coloured lymph nodes Patent blue was injected around the primary tumour to induce the discolouration of further lymph nodes.

Our observations suggest that the procedure when the vital stain is injected into the plexus areolaris located in the region of the areola mammae is far simpler, as identical lymph vessels and lymph nodes get discoloured in the axilla.

In addition to its role in the identification of the sentinel lymph node, the vital stain injected into the skin of the areola signalizes lymph node metastasis by visualizing lymphostasis in the form of a pathological outline of the lymph nodes of the breast.

The data obtained in the 5-year follow-up suggest that the status of the axillary lymph drainage clearly indicates the likelihood of distant metastases and it can also account for the observation made by Gardner concerning the increased mortality rate of breast cancer in the first 7 postoperative years.

Can the mortality of breast cancer be reduced?

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Aim: The mortality of breast cancer remains relatively unchanged by the therapeutic advances of the past 20 years. The aim of this study was to investigate the mortality curves of breast cancer and compare these with colorectal cancer.

Material and methods: All cases of breast cancer from 1980–1996 were identified and the pathological stage derived. Cause of death was determined from the Registrar General. The yearly proportional mortality (YPMR) due to breast cancer was determined by tumour size and nodal status. From an existing database of long-term follow-up of colorectal cancer with accurate stage, similar survival curves were drawn.

Results: The YPMR remained almost constant over a 10-year period of follow-up for tumours that were node negative, or less than 30 mm. This reflects a constant mortality rate which does not decrease with time. For larger tumours and node positive tumours there was a rise in the YPMR for the first 3 years which then tailed off. This curve resembles the curves of mortality from colorectal cancer, which show an exponential decay for each Dukes' stage.

Conclusions: The mortality for most cases of breast cancer is a continual constant ebb and any novel treatment will not show an improvement in mortality for many years. In addition, the optimal method of reducing the mortality will involve a stage migration to a better prognostic grouping, such as expected with mammography.

The disorders of peroxide-antioxide balance of an organism in breast cancer

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Introduction: Breast cancer is still the leading cause of cancer mortality in women. New diagnostic markers of the breast cancer are still being developed. The aim of this study was to estimate a peroxido-antioxide balance in breast cancer.

Material and methods: We analysed two groups of patients. The first group was 48 women with breast cancer. They were treated by modified radical mastectomy (removal of only the breast and the axillary lymph nodes). In the second one (the control group) there were 15 women, with diagnosis of benign dysplasia. They were treated by excision. The patients did not have other complaints. Assay of peroxido-antioxide balance was performed on the basis of lipid peroxidation products in plasma (MDA – malonyl dialdehyde, CD-conjugated dienes, HPETE-lipid hydroperoxide) and the activity of free radical scavengers, such as superoxide dismutase (SOD) in erythrocytes and glutathione peroxidase (Gpx) in whole blood. Conjugated dienes-CD and lipid hydroperoxide (HPETE) were marked using the method of Buege's and Augusta in Warda's modification. The concentration of malonyl dialdehyde (MDA) were determined using the method of Okava and Yagy. The activity of glutathione peroxidase (Gpx) were determined using method of Paglia and Valentine's and the activity of superoxide dismutase were determined using the Kawaguchi's method. In both groups above-mentioned markers were determined twice before surgery and 10 days after the operation. The results obtained were statistically analysed.

Results: The average age of patients was 49 years (range 33–68 years). In approximately 65 per cent of patients with the breast cancer the level of lipid peroxidation products was significantly higher before operation than after it. On the contrary the levels of superoxide dismutase (SOD) and glutatione peroxidase (Gpx) in approximately 70 per cent of cases were higher before the operation. In patients with a diagnosis of benign dysplasia, we have not noticed changes of the levels of lipid peroxides product and levels of SOD and Gpx. In the group of women with breast cancer there were statistically significantly higher levels of lipid peroxides and the levels of SOD and Gpx than in group of women with diagnosis of benign dysplasia.

Conclusions: Our results showed that: breast cancer increased the process of lipid peroxidation in an organism and increased of the activity of free radicals scavengers; the determination of levels of lipid peroxidation products and the activity of SOD and Gpx may be of considerable importance in diagnosis of breast cancer.

Correlation of biochemical tumour markers to conventional pathologic features in primary breast cancer

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The aim of our study is to analyse the relationships of conventional pathologic factors to serum and cell biochemical markers in breast cancer patients. A total of 574 patients were operated on for primary invasive breast cancer at our Institute from September 1996 to October 1997. The serum levels of CEA, CA 15·3, TPA-M and Thymidine Kinase (TK) were measured prior to surgery in all patients. Surgical specimens were processed for routine pathology (histological typing, grading and staging) and for cytosol analysis (oestrogen and progesterone receptors, p53 peptide, uPA, EGFr, erbB2, bcl2 and BAX determination). Disease relevant anamnestic and clinical data were also recorded.

Of the 574 patients studied, 63 per cent were node negative, 71 per cent postmenopausal, 88 per cent had tumour less than 5 cm in size (T_1-T_2). Estrogen receptor positivity was found in 61 per cent whereas progesterone receptor positivity in 72 per cent of the tumours. There were 95 cases (21 per cent) with histological grade I tumour.

The p53 protein and BAX levels correlated positively with tumour size, histological grade and lymph node state. The serum levels of CEA, CA 15·3, TPA-M and TK correlated with pathologic tumour stage. There was a significant difference in pre- and postmenopausal breast cancer patients in the serum level of TPA-M and cytosol level of BAX.

These results may give prognostic significance in breast cancer, but this needs to be proven by careful follow-up of patients included in the study.

Myxoid fibroadenomas of the breast

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Three cases of this rare entity which occurred in three young women of 36, 25 and 20 years of age are presented.

All of them consulted for palpable nodules with benign findings in breast ultrasonography and mammography. The fine needle aspiration cytology were informed as fibroadenoma. The reasons for the excision were: pain, big multiple nodules and familial breast carcinoma antecedent.

In two cases, the patients presented a facial multiple spotty pigmentation and one of them presented with ocular and labial pigmentation and an exotosis in the left parietal region (Carney's Syndrome). In this case the patient's grandfather had the same skin pigmentation.

An echocardiogram and a complete endocrine functional study were performed to the patients which were absolutely normal.

In 1986, Carney reported a familial syndrome transmitted as an autosomic dominant trait which consisted in spotty pigmentation of the face and oral mucosal, cardiac myxoma and endocrine overactivity. In 1991, he published myxoid changes in mammary stroma that were a specific pathological marker of a determined human genome.

This lesion is benign but it is important to recognize it because it may be associated to other grave syndromes as cardiac myxomas which are potentially lethal, so it is necessary to perform a thorough investigation of these patients and their families.

Breast conserving therapy in stage I and II breast cancer

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The aim of our work was to compare effects of modified radical mastectomies (Madden, Patey) and breast conservation therapy on breast recurrence and overall survival.

Over the 5-year period from 1 January 1989 to 31 December 1993 at Surgical Clinic in Niš 142 women were treated for T_1 and T_2 breast cancer. Of the 142 women, 94 were treated by modified radical mastectomy and 48 had received breast conservation therapy. These women were separated into two groups. There were no significant differences between the groups in tumour size, incidence of axillary node involvement, histology grading ($P>0·05$). In general women treated for breast cancer with breast conserving therapy were younger, 42 years to 48 years treated by modified radical mastectomy.

Two of 48 patients had locoregional recurrence: one of them at the operation wound, the other elsewhere in the breast, histology was lobular type contrary to prior ductal carcinoma and was treated with radical mastectomy-modification of Madden.

Two of 94 patients who received modified radical mastectomy had locoregional recurrence: both of them on the chest wall.

The overall survival rates in modified radical mastectomy patients and breast conserving group were respectively 89·3 per cent and 91·1 per cent.

These results indicate that there were no significant differences between two groups in locoregional recurrence and overall survival in T_1 and T_2 breast cancer.

Breast reconstruction practice in the National Institute of Oncology, Budapest

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In Hungary, breast cancer is the most frequent malignant disease of women. Reconstructive surgery plays an essential role in the rehabilitation of these patients. All reconstructive techniques are available at our Institute. Satisfactory cosmetic results can be achieved either by local, pedicled and free flaps or reconstructive expander and implant system. Their combination is also used if needed. Criteria of the surgery of choice are demonstrated. Future trends in reconstructive breast surgery are outlined.

Possibilities of conservative therapy in Paget's disease

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Paget's disease constitutes about 1 per cent of breast cancers (1) and its main characteristic is the occurrence of Paget's cells. From the point of view of biological growth the disease is divided into preinvasive form concerning only the nipple and invasive one spreading into the gland's parenchyma as well as from inside towards the nipple (epidermotropism). The accepted way of treatment is radical and total mastectomy, conservative operations being still controversial for many therapeutic centres. Our study comprised 28 patients treated in the years 1989–1994. Radical surgery was performed in 25 patients and conservative in three women. In 23 cases we had to deal with intraductal component and in three with infiltrating component of Paget's disease. Metastases to lymphatic nodes were observed in three patients. Five-year survivals amounted to 91 per cent in patients with intraductal component (2), 51 per cent in patients with infiltrating component (3) and in patients with lymphatic nodes metastases only 30 per cent (4). Local recurrences occurred in four cases after radical surgery, while after conservative operations in two patients. The first patient shown to have infiltrating components by histopathological examination, without metastases to the lymphatic nodes underwent telegammatherapy radiotherapy in whom a recurrence developed after 6 months. She underwent total mastectomy. The second patient was operated on repeatedly after histopathological detection of a large intraductal component and the presence of neoplasm within the surgical section. Radical mastectomy was performed in her. The last patient after conservative operation showed to have preinvasive form and has been under observation for 5 years. Conservative operations in Paget's disease should be performed in the preinvasive stage since the therapeutic and cosmetic effect is the best then.

Ulcerating breast cancer (UBC)

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The aim of this work is to show our experiences and results in UBC treatment.

In our Department, between 1988 and 1997, 478 (3·75 per cent) of radical mastectomy because of carcinoma of the breast. The patients with UBC were 52 (11 per cent) and they all have been surgically treated. Later on, 28 (54 per cent) of them were subjected to radiotherapy, and chemotherapy got 20 (38 per cent). 88 per cent were verified with present metastatic invasive ductal carcinoma changes in axillary lymphonodes. Twenty-four patients (46 per cent) were those who were only subjected to surgical treatment. Five patients (21 per cent) were living longer than 5 years; nine patients longer than 3 years (37 per cent) and over 1 year 17 patients (71 per cent). Twenty-eight patients (54 per cent) had radio- and/or chemotherapy where there were seven patients (25 per cent) who were living more than 5 years, 13 (46 per cent) more than 3 years, and 20 (71 per cent) longer than 1 year. All were female. Average age was 66 years and all of them were in postmenopause age. They were under review every 2 months regularly during the first year, and later on every 6 months.

From early postoperative complications we have seven wound infections which we solved by conservative methods.

Conservative postoperative treatment with our material has not had a decisive influence as to longer survival having in consideration about patients of older, wherein the only radical mastectomy gave good results.

Palpable breast masses: comparison of ultrasound and mammography in differentiating malignant and benign origin

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Aim: To compare High-resolution Ultrasound (US) and Mammography in differentiating palpable benign and malignant breast masses.

Material and methods: Two hundred and twenty-one palpable breast lesions of 120 patients aged 30–84 years were examined with X-ray mammography and high-resolution sonography. Benign or malignant characteristics of masses were established by both modalities. US guided FNAB was performed from all nodules and a 6–36 months follow-up was made for cystic lesions. The final diagnosis was obtained histologically for all malignancies. US and mammographic classifications were compared with the histologic diagnosis.

Results: Final diagnosis revealed 124 cysts (56 per cent), 30 carcinomas (13·5 per cent), 54 fibroadenomas (24 per cent), four benign phyllodes tumours, six mastopathic nodules, three fat necrosis. The malignant lesions included infiltrating ductal carcinoma (n=24, 80 per cent), infiltrating lobular carcinoma (n=3, 10 per cent), mucinous carcinoma (n=3, 10 per cent). Nineteen (63 per cent) of the malignancies had less than 2 cm maximum diameter. Sensitivities and specificities in diagnosing malignancies were not statistically significantly different for US (90 per cent, 81 per cent) and mammography (85 per cent, 95 per cent). US with FNAB yielded 100 per cent sensitivity and specificity in this study.

Conclusions: High resolution ultrasound is a comparable method to mammography in characterizing palpable breast masses, especially, if combined with US guided FNAB.

Cowden's Syndrome

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Cowden's Syndrome or multiple hamartoma syndrome is a rare autosomal dominant premalignant syndrome characterized by orocutaneous hamartomatous tumours, gastrointestinal polyps, abnormalities of the breast, thyroid gland and genitourinary system. The gastrointestinal polyps are generally benign and malignant transformation are seen very rarely. However, there are serious potential of malignancy in the breast and thyroid gland.

We present a patient with Cowden's Syndrome who underwent mastectomy operation 5 years ago with previously nondiagnosed Cowden's Syndrome in another centre. This patient was presented to our hospital with the complaints of anal fissure. After physical examination and investigations, the patient was diagnosed as Cowden's Syndrome. We found oral mucosal, gingival and cutaneous papillomas, gastrointestinal polyps, fibrocystic disease and malformation of the nipple of the other breast, and nodular goitre. It was learnt that her sister had died because of breast cancer.

If the physician remembers the Cowden's Syndrome in patients presenting with orocutaneous lesions, gastrointestinal polyps, thyroid and breast disease, it may lead to the early diagnosis and treatment of cancer.

A new concept in wound healing: the management of wounds with negative pressure therapy

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Aim: We present the early results of a study evaluating the role of negative pressure therapy (NPT) in the management of various wounds. NPT is an exciting new concept in wound care which is simple to use and confers many benefits. It is claimed that it reduces oedema, increases blood supply, reduces bacterial colonization, promotes rapid formation of granulation tissue and mechanically closes the wound. Healing rates are dramatically improved. This study assesses these claims.
Material and methods: Two hundred wounds were treated with NPT, mostly as an adjunct to surgery, pre- and postoperatively. Both acute and chronic wounds were included in the study. Acute wounds included lower limb trauma, infected wounds, burns, necrotizing fasciitis, fasciotomies and pretibial lacerations. Chronic wounds included pressure sores, leg ulcers and miscellaneous non-healing wounds. All wounds were assessed clinically, photographed and mapped for size before and after treatment. Tissue samples for microbiology were obtained.
Results: Overall, the majority of wounds showed a marked clinical improvement including a decrease in size and a significant reduction in quantitative bacterial counts in infected wounds. The need for fewer dressing changes together with an earlier discharge had significant resource implications. We have found little morbidity in using NPT and patients tolerated the dressings with few problems. It appears to be patient, nurse and doctor-friendly.
Conclusion: This study has shown negative pressure therapy to be of great benefit in the management of wounds, particularly in problematic cases. The mechanism of action, future applications and its use throughout all surgical specialties is discussed.

Primary retroperitoneal tumours

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Aim: The best treatment in primary retroperitoneal tumours is the total surgical resection of the mass. The most important postoperative problem is the recurrence of the disease.
Material and methods: Twenty-six patients with primary retroperitoneal tumours operated in our department.
Results: Eighteen (69·2 per cent) of the patients were male and eight were female (30·8 per cent), with an overall mean age of 43·3 years. The most frequent complaints were abdominal mass, pain, nausea and vomiting. All the patients were examined with ultrasonography (US), while 18 patients were examined with computerized tomography (CT). Four of the five patients who underwent needle biopsy under CT guidance had the diagnosis of maligant tumour. The intraoperatively measured diameters of the tumours were less than 5 cm in eight, between 5–10 cm in four and more than 10 cm in 14 patients. The histopathological distribution of the tumours among 26 cases were liposarcoma in six, leiomyosarcoma in four, malignant schwannoma in four, rhabdomysarcoma in three, angiomyosarcoma in two, chordoma in two, neuroblastoma in two, lipoma in two cases and teratoma in one case. Twenty-one cases (80·8 per cent) were malignant and five cases were benign in nature. Fourteen of these cases underwent total extirpation, while 12 cases had only biopsy of the mass. Among the postoperative complications, bleeding in four and lymphatic leakage in two patients were observed. One patient who had undergone only biopsy procedure died in the postoperative fifth day due to cardiac insufficiency (3·8 per cent). After the operation, one patient received radiotherapy, 10 received chemotherapy and seven patients received both. The 5-year survival rate was 57·1 per cent, while 3-year survival rate of the biopsied patients was 33·3 per cent.
Conclusions: The best treatment modality in primary retroperitoneal tumours is, if possible, total surgical resection. However, in our opinion, in cases of tumours not eligible for surgery, adjuvant treatment options combined with palliative resection procedures might increase the survival.

Total intravenous propofol anaesthesia (TIVA) with epidural or opiate analgesia for colorectal surgery?

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Aim: To compare differing anaesthetic and analgesic techniques on perioperative outcomes of colorectal surgery.
Material and methods: In this prospective, randomized trial, 37 patients have so far been entered into four treatment arms. All received Propofol TIVA and either inaled nitrous oxide/oxygen mixture or air/oxygen. Preoperatively patients received either intravenous morphine or epidural bupivicaine, analgesia being maintained postoperatively as patient-controlled analgesia (PCA) or by continuous epidural infusion.
Results: Peroperatively, patients who had epidurals tended to have less operative blood loss (median 710, range 200–2235 ml) than the morphine group (median 1325, range 250–2725 ml) and fewer of them were transfused postoperatively (17 per cent vs 58 per cent; $P<0{\cdot}05$). Operating time was significantly reduced in patients having epidural (median 126, range 60–280 min) compared to the morphine group (median 180, range 86–240 min; $P\leq 0{\cdot}01$). Pain relief, measured subjectively (defined as excellent/good or fair/poor) was significantly better in those who had epidural (83 per cent vs 37 per cent; $P<0{\cdot}02$). Return of intestinal function was assessed by measuring days to return of bowel sounds, first flatus and first bowel action, with trends suggesting an advantage to the epidural group. The time from operation to discharge was less in the epidural group ($0{\cdot}1<P>0{\cdot}05$).
Conclusions: The use of epidurals in elective colorectal surgery is associated with a reduction in blood loss, transfusion requirements, shorter operating time, gives superior pain relief and may afford earlier return of intestinal function and earlier discharge from hospital.

Acute low intestinal obstruction due to AIDS-associated lymphoma

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Introduction: HIV-infected patients suffer different spectrum of diseases comparing with the general population. Non-Hodgkin's lymphomas appear when there is a profound immunodeficiency. In spite of the high incidence in our practice, it is unusual to find an acute low intestinal obstruction caused by AIDS-related lymphoma. Only short reports have been published about low intestinal obstruction (LIO) caused by Kaposi's Sarcoma, CMV intestinal infection and intestinal lymphoma.
Material and methods: This is a retrospective study of the patients suffering intestinal lymphoma that caused LIO. Since 1985 four cases of LIO were treated at our institution caused by AIDS-related lymphoma. Patients were divided into two groups (two patients each one) according to CD_4-cell count: group I <200/mm^3 and group II >200/mm^3. We studied clinical status (including Karnofsky's rate and survival rate), surgical procedures and pathological findings.
Results: Aged from 28 to 39 (mean 34), all of them were male. Three of them admitted homosexual practice, another intravenous drug addiction.

	Group I	Group II
Years from HIV-infection diagnosis	>4 years (4–10)	<1 year (1–4)
Karnofsky	<50%	>60%
Ag VIH	+	–
Survival from diagnosis of lymphoma	<1 month	>6 months with chemotherapy (CHOP)

All of them were operated to solve intestinal obstructions: two intestinal by-pass (two lymphomas of ileocal area) and two colostomies (two rectal lymphomas). Pathological study: two high-grade B-cell lymphoma, one high-grade T-cell lymphoma, one high-grade 'null' lymphoma.
Conclusions: 1. Survival rate was related to the CD_4-cell count and clinical status of these patients. 2. Chemotherapy can improve survival in selected patients. 3. Surgery is most often palliative (to solve intestinal obstruction).

The use of unilateral pudendal thigh flap in the treatment of complex rectovaginal fistula

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Introduction: A tissue transposition procedure is presented in which a unilateral neurovascular pudendal thigh flap is used to correct two cases of complex rectovaginal fistula.
Case reports: Case 1: A 49-year-old woman presents with a complex rectovaginal fistula caused by the prolonged use of analgetic suppositories in combination with corticosteroid enemas. Just proximal of the fistula there is a circular stenosis. A derivative colostomy is performed and two months later a unilateral pudendal thigh flap is performed. Anal dilatation is done twice before closure of the colostomy. No recurrence seven months later, no incontinence, no rectal dyschezia.
Case 2: A 27-year-old woman presents with a complex rectovaginal fistula after vulvotomy (narrow introitus). A unilateral pudendal thigh flap is performed without complication and without protective colostomy. Normal anal sphincter function and a normal introitus vaginae without recurrence after 10 months.
Operative technique: The fistulous tract is excised after an inversed T-incision is made in the posterior vaginal wall. The rectal mucosa and muscle are closed in sequential order. A large fasciocutaneous flap borne on a subcutaneous pedicle supplied by the posterior labial arteries and containing posterior labial branches from the pudendal nerve is tunnelled under the labium mayosa and rotated in the defect.

The causes of rectovaginal fistulas are multivaried but mainly caused by obstetric trauma. The rectovaginal fistulas are classified as simple or complex. Their treatment is based on this classification. Three mean approaches are possible: local repair, transabdominal repair and tissue transposition procedures. Simple fistulas are in general successfully treated by one of the local repair procedures. In complex fistulas abdominal procedures and tissue transposition procedures are recommended, mainly due to the presence of infected and poorly vascularized surrounding tissues resulting in poor wound healing.
Conclusion: The use of a unilateral pudendal thigh flap seems to be a successful and reliable alternative to treat complex rectovaginal fistulas. The flap is robust and sensate with a reliable blood and nerve supply.

Second primary malignancies: clinical approach and surgical results

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Aim: The main reasons for the growing incidence of second malignancies after primary neoplasms are the carcinogenic effect of antiblastic treatment, the widespread use of immunosuppressive drugs and the immunosuppression typical of chronic lymphoproliferative disorders. This study aimed to determine possible clinical and prognostic differences between patients with primary hematologic and primary non-hematologic tumours.
Material and methods: We studied 42 patients in whom second malignancies developed, in 16 cases after primary haematological and in 26 after non-hematological tumours. In both groups we assessed the pathologic stage of the first tumour at diagnosis of the second; the time elapsing between the two malignancies, the incidence of postoperative complications and survival.
Results: Hematologic tumour group: on diagnosis of the second tumour 62·5 per cent of patients had attained complete remission but 37·4 per cent had only a partial response or disease progression. A mean 4·5 years elapsed between the two malignancies. Staging identified second tumours in stages I–II in 56·2 per cent of cases and III–IV in 37·4 per cent; radical surgery, performed in 62·5 per cent of patients, led to 12·5 per cent morbidity. Overall 3-year survival was 31·2 per cent.

Non-haematological tumour group: on diagnosis of the second tumour all patients showed complete remission of the first tumour. A mean 6·6 years had elapsed between the two malignancies. Staging identified second tumours in stages I–II in 70·2 per cent of cases; radical surgery, performed in 61·5 per cent of cases, led to 15·3 per cent morbidity and 3·8 per cent operative mortality. Overall 3-year survival was 46·1 per cent.
Conclusions: Patients with haematological tumours have a shorter mean interval between the first and second malignancies; a higher percentage of second tumours in advanced pathological stages and shorter survival. These patients' less favourable prognosis seems to depend upon the high percentage of first haematological tumours uncured (about 40 per cent) and upon the severe persistent immune system defects. Although these defects are related to treatment they also closely reflect the biological features of the haematological malignancy (Hodgkin's or non-Hodgkin's lymphoma and chronic lymphoid leukaemia).

A contribution to the study of influential factors on postoperative malnutrition

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Aim: The surgical act, in spite of your curative intentions, behaves like an aggression, if this too intense or the biological response results inadequate postoperative complications appear. That this process will be favourable for the patient, the nutritional state that the patients present before a surgical intervention it is responsible to a large extent. In order to demonstrate the correlation between the operation and alteration of the nutritional parameters, it is necessary to identify nutritional and non-nutritionals factors, that could have a malnutrition prediction value.
Material and methods: Two hundred and six patients have being studied who interrelated independent variables have been used: nutritional parameters, age, sex, risk factors, type of pathology, treatments effected according to process, have been studied complications presented and other. Biochemical, anthropometric and immunological parameters, have been to include at the preoperative and postoperative stage of the patients. The obtained data allows the definition of the nutritional state of each patient.
Results: The presence of malignant disease, integrity of intestineal anastomosis, degree of operative contamination and age, present a relationship to of postoperative malnutrition. We have been able to prove the validity of the known predictors of morbidity and mortality postoperative. We have been obtained a forecast formula, to determine the greater surgical risk patients, in which intervene the following parameters: albumen, transferrin, cancer, and the degree of surgical contamination.
Conclusions: The nutritional state at with the patients arrives to the operation, has a great influence in the results. An important decrease in the visceral proteins in the postoperative period has been observed. Being at 48 hours postoperatively, the moment of minimum levels. At seven days recovery is observed. It is remarkable that neither anthropometric on immunologic parameters, take part in the forecast formula obtained by logistics regression that anticipates the degree of postoperative malnutrition. It is necessary to effect a nutritional preoperative valuation, that will warn us of possible postoperative complications and even leading to modification of timing of therapy.

The effects of early postoperative enteral feeding methods on immune system

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In this study, the effects of early postoperative enteral feeding methods on immune system and the role of such methods in decreasing septic complications were investigated and compared to parenteral feeding methods in a population of patients undergoing upper gastrointestinal surgery. A total of 40 patients were divided into four groups each consisting of 10 patients and three groups were given different feeding methods. Patients who received previous chemo or radiotherapy, and those who had diabetes mellitus or malnutrition and those under immunosuppressive treatment were excluded from the study group. The first group received postoperative immunostimulant enteral formula, the second group received standard enteral formula, the third group received pronteral branched chain aminoacid solution in addition to standard dextrose and lipid solutions. The fourth group received no special feeding support and was used as a control group. Patients were followed up for signs of septic complications in the first 10 days of postoperative period (fever, ESR, WBC count, signs of wound infection, lung infection, peritonitis and sepsis). In addition plasma IgG and IgM, total lymphocyte counts, B lymphocyte counts, CD4/CD8 ration, T-lymphocyte and natural killer (NK) cell activities and plasma IL-2 levels were determined in the postoperative 1, 4, 7, 10th days.

The first and second groups had no septic complications but 20 per cent of the third group and 30 per cent of the fourth group demonstrated signs of septic complications. The first group had a higher T-lymphocyte count NK cell activity and IL-2 levels than second group and this difference was statistically significant. The first and second groups had a higher IgG, IgM, CD4/CD8, activated, T-lymphocyte count, NK cell activity and IL-2 levels compared to third group and this result was also statistically significant. The third group had higher IgG and IgM levels than fourth group but T-lymphocyte parameters did not differ significantly between the two groups. Septic complications were significantly lower in first three groups compared to control group. As a result early postoperative enteral feeding is superior to parenteral feeding methods and to control groups in terms of prevention of septic complications. Immunostimulants used in enteral feeding can improve immunological parameters although a significant clinical benefit has not been observed.

Management of a fulminant colitis in a neutropenic patient infected with human immunodeficiency virus (HIV)

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Zidovudine (AZT) treatment induces neutropenia in human immunodeficiency virus (HIV)-infected patients, however, neutropenic colitis has been scarcely described in this group. Management of neutropenic colitis is a matter of debate, medical or surgical? Which is the timing for surgery? We present a case that illustrates such controversial and rare clinical situation.

A 38-year-old, heterosexual, non-drug abuser, HIV-infected, male with with mild neutropenia due to AZT therapy arrived at our hospital complaining of epigastric pain, temperature and vomiting without diarrhoea for 36 hours. He had started AZT treatment due to his low CD4+ cell count (200/mm^3) and 8 months before his colitis, he abandoned such therapy because of gastrointestinal intolerance and a neutrophil count of 900/mm^3. At hospital, the physical examination revealed a conscious patient with generalized abdominal discomfort, voluntary guarding without rigidity and tachycardia. On abdominal CT scan the most important finds were right colon thickening and free fluid. Neutrophil count was 456/mm^3 with a white blood cell count of 1200/mm^3. The patient was initially managed at the intensive care unit where a peritoneal lavage showed Gram-negative bacilli. Despite of broad-spectrum antibiotics and aggressive medical therapy, the patient got worse and was operated on 17 hours after his admission with coagulopathy and inotrophic support. A right hemicolectomy was performed due to caecal necrosis; unfortunately, the patient died 8 hours after. The histological examination of the specimen only revealed cocci and bacilli with no cytomegalovirus intranuclear inclusions.

Although abdominal examination of HIV-positive population is somewhat difficult, these, as oncologic neutropenic patients, belong to a high risk group to develop septic shock. Early surgical approach after a positive CT scan and peritoneal lavage confirmation of enteric bacteria by Gram dye could offer a better outcome among patients with neutropenic colitis. This is to our knowledge the second report ever in the literature of neutropenic colitis among HIV patients.

Is the surgical procedure the right approach for totally implantable venous device (TIVD) placement?

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Introduction: Totally implantable venous devices (TIVD) are frequently utilized in patients requiring prolonged intravenous therapy or repeated blood sample analyses. Percutaneous subclavian vein introduction is the method of choice but pneumothorax, or arterial puncture frequently occurs at moment of insertion.

Aim: To report our experience with surgical approach in order to assess the better way for TIVD placement.

Patients and methods: Data include TIVD inserted between November 1995 and November 1997. Age, sex, pathology, way of insertion, mean duration, intra and postoperative (until 30 days) complications of patients operated on were considered.

Results: During a 2-year period 122 patients were operated on for TIVD insertion. The patients were 75 males and 47 females aged from 29 to 79 years (mean age 59·5). One hundred and twenty-one TIVD were inserted for oncological reasons and one for TPN. All 122 TIVD were inserted by surgical procedure under local anaesthesia with small sedation, in 94 patients (77 per cent) by cephalic vein, in 13 (10·6 per cent) by axillary vein, in four by external jugular vein, in two (1·6 per cent) by internal jugular vein, in six by right gonadal vein, in one by coraco-brachial vein, in one by long saphenous vein and in 1 by vena cava. The mean duration was 456 days. No intra- or postoperative complications were recorded.

Conclusion: These results suggest that surgical procedure for TIVD placement is safe and reliable. Cephalic vein is the method of choice. Difficult vascular access may be utilized without any risk by experienced surgeons.

How clean are sterile instruments? parameters and testing and clinical data

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Introduction: Bioburden in biofilms on surgical instruments cannot be detected if not visible. Data must be collected for cleaning modalities under the condition of complex filigran endoscopic instruments.

Material and methods: Different instrument parameters (surface, material, design, temperature, dry or wet test soil) were investigated in this project. Native blood as test soil seemed most adequate for comparison. It was recovered from surface by Sodium-dodecyl-sulfate (SDS) and the quantity of recovery (percentage) was analysed with the modified OPA-method.

Results: Cleaning performance was measured for clinical laparoscopic instrument cycles allowing to differentiate between working tip, tubes, handles. More than 95 per cent of native blood was regained from standardized test bodies. Significant differences in recovery could be determined for different surfaces of dental drills and non-dismantable arthroscopic instruments confirming the thesis that smooth surfaces and dismantability eases decontamination. The SDS/OPA method was sensitive, specific and reproducible.

Conclusion: *In vitro* testing to compare different models for test soils and laboratory methods of decontamination will be done next in this project as native blood is not suitable for daily routine in sterile supply. Validation of automated cleaning with washer/disinfectors depends on precise measurement of process parameters. More data about biofilms on frequently used instruments (arthroscopy, ENT, laparoscopy, neuroscopy, urology) must be obtained.

Extragonadal endometriosis: a non-anecdotic pathology for general surgeons

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Aim: Highlighting the importance that knowledge of the different clinical manifestations that extragonadal endometriosis may present for general surgeons.
Patients and methods: We present four cases treated for extragonadal endometriosis, from the 1698 (0·23 per cent) major surgery performed at our Service between March 1996 and December 1997.
Results: Cases 1 and 2 Two women, aged 42 and 46, who had undergone a caesarean, seven and 19 years earlier, respectively, presenting through palpable and painful tumours, mainly during menstruation, located beneath the scar from the caesarean In the first case, neither the US, the CT nor the fine needle biopsy cytology (FNBC) provided good diagnosis, whereas in the second patient, the clinical diagnosis was an irreducible laparotomic hernia Following the excision of the tumours, histological diagnosis revealed endometriosis in both cases

Case 3. Patient aged 31, with no gynaecological background whatsoever, who came to surgery complaining of a blueish umbilical tumour, which was painful and secreted blood during menstruation The FNBC did not prove conclusive, but the suspicion of endometriotic nodule was confirmed by histology following its excision.

Case 4· Patient aged 42, who had undergone a hysterectomy and a right salpingo-oophorectomy two years before and did not show any intestinal symptoms at all, she was operated for a tumour in the left ovary (confirmed by US and CT), with an extramucosa tumour then being detected in the sigmoid colon, hence a left salpingo-oophorectomy and sigmoid colectomy were performed. The histological result was ovary and intestinal endometriosis
Conclusions: Extragonadal endometriosis is a disorder with rather more than anecdotic frequency for general surgeons, with great clinical variations and for which the only certain diagnosis is by means of histological studies.

Occupational risk of intraoperative HIV-infection of surgeons in Ukraine

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Rapid growth of the number of HIV-infected patients is observed today in most of the nations around the world and in Ukraine as well It is natural, that respresentatives of this contingent are more and more often admitted as surgical patients, considerably increasing the risk of contamination of surgeons.
Aim: Probability of intraoperative contact of Ukrainian surgeons with human immunodeficiency virus and the occupational risk of their HIV-infection was studied
Material and methods: I – Prospective study of the frequency of detected surgical glove damage (SGD) by way of postoperative polling among the surgeons using modified questionnary of Hussain (385 interventions) II – Determination of undetected SGD with the aid of air-immersion–water-submersion tests (330 surgical gloves after 55 randomly chosen surgeries) III – Determination of the risk of occupational infection of the surgeon as the result of probabilities of SGD while operating on the HIV-infected and frequency of seroconversion.
Results: Visible SGD have been reported by surgeons after 57 surgeries (14·8 per cent). Instances of occult perforation of the gloves of operating surgeon have been reported after 30 surgeries (54·5 per cent) Thus, total frequency of suboperative SGD appeared to be comparable with the numbers quoted in foreign literature (12–80 per cent) and attained 69·3 instances of failure per 100 surgeries According to our calculations ave
age statistical risk of intraoperative HIV-infection of the Ukrainian su
geon remained within the range of $8{\cdot}18 \times 10^{-7} - 1{\cdot}64 \times 10^{-4}$. The sam
index under the conditions of our clinic exceeded the national index b
185 times and attained $1{\cdot}51 \times 10^{-4} - 3\,02 \times 10^{-2}$ The reason for th
appeared to be a rather high percentage of parenteral drug addicts (13
per cent) among the patients in which clinical-immunological signs
HIV-infection have been found (32·8 per cent) In the event of exclusi
operation performed on the 'risk group' patients the probability of infe
tion of the surgeon increased by 7·5 times and attained critical values
$1\,14 \times 10^{-3} - 2{\cdot}27 \times 10^{-1}$.
Conclusions: The degree of probability of professional HIV-infection
surgeons is in direct proportion to the number of AIDS 'risk grou
patients operated on and the frequency of SGD occurrence. In order
prevent uncontrolled nosocomial spread of HIV-infection it is necess
to. 1) Promote HIV-awareness among the surgical teams and introduce
obligatory procedure of preoperative identification of the risk gro
patients; 2) Elaborate measures eliminating evident SGD and acciden
suboperative injuries of surgeons' hand and a system of the means
urgent prophylaxis of contact HIV-infection, 3) Elaborate reliable te
systems for timely detection of occult SGD; 4) Improve techniques
operative intervention in order to avoid intraoperative exposure of medi
staff to virotropic media of the patient.

Snake bites: effectiveness of antiviperin serum and surgery

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Vipers inhabit all of the European Continent except for the North Po
However, the undoubtable epidemiological interest that represents its
ing, scientific papers are scarce. On the other hand, the use of antivipe
antidote remains polemic
Aim: To analyse our therapeutic results with a systematic administrat
of antiviperin serum.
Material and methods: In the last 10 years, 34 patients have b
accepted due to viper bites According to Wood-Parish classificati
stage 0 (4), stage 1 (6), stage 2 (20) and stage 3 (2) In 32 patie
antiviperin serum was administered (V. Aspis, V Berus, V. Ammodyt
in the first 24 hours Skin was infiltrated with 1 ml around the bite,
4 ml intramuscular injection At the same time, antitetanic and antibio
protection were administered. Neither wound infection nor mortality
seen. Surgery was only necessary in one case (stage 3) due to comp
ment syndrome affecting the left arm that needed fasciotomy of arm, fo
arm, wrist and second finger. Functional and aesthetic results were go
Conclusions: 1 – Antiviperin antidote used in an early phase, avoids
progression to advanced stages. 2 – Surgery is only necessary in so
cases like shown above.

Reduced amounts of total protein in artificial wounds of alcoh abusers

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Aim: Alcohol abusers have increased risk of complications following s
gical procedures However, little data are avilable on the impact fr
alcohol abuse on the wound healing process
Material and methods: Sixteen patients with a daily median consu
tion of 240 g alcohol were compared with 30 elective surgical patie
(herniotomy, cholecystectomy, colorectal resections) consuming less t
60 g alcohol daily All patients had normal plasma levels of standard h
atic and renal assays Collagen and total protein accumulation in wo
granulation tissue was evaluated from the deposited amount of hydro

proline (HP) and proline (PR) in two subcutaneously implanted ePTFE tubes (Impra®, pore size: 90–120 μm). Following removal of the tubes on day 10 and hydrolysis of the deposited tissue, the content of HP and PR was determined by a high performance liquid chromatography assay and expressed as amount per length of ePTFE.

Results: PR was significantly lower in the group of alcohol abusers median 720 nmol/cm (inter-quartile range: 687–813) than in the group of surgical patients 884 nmol/cm (717–1062), *P*<0·05. HP in the group of alcohol abusers and surgical patients were 11·3 nmol/cm (4·6–15·9) and 11·1 nmol/cm (6·3–15·3), n.s., *P*=0·54.

Conclusion: The results indicate that the healing process is generally slowed in alcohol abusers as expressed by the reduced amount of total protein deposited in granulation tissue. This data may partly explain why alcohol abusers have an increased risk of wound complications. We are currently testing if 2 months of alcohol abstinence in chronic alcohol abusers reverses the depressive effect on wound healing.

Pilonidal sinus: 'jeep disease' or 'jean disease'

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In 1944, Dr. Louis Buie presented his classic paper in which he named pilonidal sinus as 'jeep disease'. Following this paper, it has been reported in several articles that the disease is frequently met in military personnel and that it is due to such factors as the use of jeep and other vehicles, excessive physical activity, heavy military clothes and equipment, and subsequent sweating.

Half a century later, we observed in the Middle East Technical University Medical Centre (METU-MC) that pilonidal sinus is commonly seen in students who wear jeans in their daily life. Jeans cover the legs and gluteas tightly, prevent air circulation, and cause increased sweating. Thus, we analysed our pilonidal sinus patients by questioning them about their clothing preference.

Results: Thirty-seven students with pilonidal sinus were admitted to METU-MC in an eight-month period (83·8 per cent), presented a pilonidal abscess at the first admission. 86·5 per cent of the patients answered our question about their clothing preference as they regularly or frequently wore jeans.

	Regularly (7 days/week)	Frequently (4–6 days/week)	Sometimes (1–3 days/week)	Never (0 day/week)
Jeans in daily life	27 (46·0%)	15 (40·5%)	2 (5·4%)	3 (8·1%)

Conclusions: There seem to be two important factors for developing pilonidal sinus; young age and personal hygiene. University students are already in the peak age group and if they do not care for personal hygiene, they may develop pilonidal disease.

In a population study of Minnesota college students, pilonidal sinus was noted at routine physical examination in 1·1 per cent of males and 0·11 per cent of females. We have 11 991 male students and 6459 female students in our university. It means a potential of approximately 200 pilonidal sinus patients and more than 1000 dressings. It is hard to say that wearing jeans is an independent factor for pilonidal disease. However, our observation made us think that such clothing may cause pilonidal sinus to develop, and at least can render an asymptomatic pilonidal sinus to a symptomatic one.

Bone disease after extensive gastroenterological operations: preliminary report

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It has been shown that resective procedures within the alimentary tract such as total gastrectomy or extensive resections of the small bowel result in the development of bone disease. Mechanisms which cause the bone loss after those operations are complex and still not fully elucidated. Recent studies revealed that neither calcium, nor vitamin D substitution can prevent the development of it, thus these deficits are not responsible for postgastrectomy bone disease. Little is known about the state of bones after oesophagectomy, pancreato-duodenectomy and colectomy.

Aim: The evaluation, which of the extensive resective procedures within the alimentary tract leads in the early postoperative period to the bone loss.

Material and methods: Six patients after transhiatal oseophagectomy (OES), ten after total gastrectomy (GX), nine after pancreatoduodenectomy (PD) and five after total colectomy (TC) were examined. Thirty patients awaiting the same type of surgery constitute the control group. Twenty-four to 36 months after surgery, bone stiffness (BS) of the calcaneus was measured (Achilles,* Lunar) and bone mass defect (BMD) as compared with the control group, was calculated. All data were subjected to ANOVA, followed by a Student *t*-test or *U* Mann–Whitney test as appropriate.

Results: Bone Mass Defect (BMD) after different extensive resections within the alimentary tract expressed in percentage of the expected value in healthy individuals matched for age, sex and body mass index.

	OES		GX		PD		TC		Total	
	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery
n	6	5	10	8	9	8	5	9	30	30
BMD*	10·50 ±1·38	17·00 ±4·50	8·80 ±1·92	12·00 ±3·41	10·00 ±2·19	20·63 ±3·39	11·60 ±3·19	10·00 ±2·16	9·97 ±1·05	14·53 ±1·73
P	0·2373		0·3989		0·0114*		0·6762		0·0277*	

*Data are mean values ± SEM.

Conclusions: In the pooled group of patients after above mentioned operations the bone mass defect was greater than observed in those awaiting similar operations. However, only in patients of the pancreatoduodenectomy groups the difference was significant (*). After colectomy an insignificant improvement was observed. Long-term studies based on more objective methods should show whether colectomy in patients with inflammatory bowel diseases improves the bone state indeed.

The use of carbon dioxide laser to control cutaneous limb recurrence from malignant melanoma

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Surgical excision of cutaneous malignant melanoma metastases is only practical when the number of lesions is small. In lesions confined to the limbs, isolated limb perfusion (ILP) has been our treatment of choice for the past 10 years. This, however, is not possible in all patients. We present our experience with carbon dioxide laser ablation as an alternative treatment in the control of cutaneous metastases in such patients. Between September 1992 and November 1996, 29 patients (20 female and nine males) underwent a total of 57 laser treatments. The lesions were situated on the face, chest, arm and leg. The number of lesions per patient ranged from two to 43 nodules. A Sharplan 1030 portable carbon dioxide laser was used. All procedures were carried out under general anaesthesia. Each lesion was destroyed using a focused laser beam of 10–20 watts with a beam size of 0·5–1·0 mm. Twelve patients have had multiple laser treatment in the attempt to control local disease, the most being seven treatments in one patient. At a mean follow-up of 18 months, six patients have died from the disease. In the 23 patients who are alive, 18 have had no recurrence of the disease and five have had partial control of local disease. Our experience suggests that carbon dioxide laser ablation of cutaneous metastases is a minimally invasive procedure which gives effective palliation.

Lymphatic mapping to identify sentinel node in patients with malignant melanoma

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Controversy still surrounds elective lymphadenectomy for treatment of patients with clinical stage I malignant melanoma. We have assessed a new technique first described by Morton *et al.* which allows identification of patients with involved lymph nodes who may benefit from elective lymphadectomy. The technique is based on the hypothesis that metastases occur along the lymphatic channels to a sentinel lymph node (the draining lymph node nearest the site of the primary malignant melanoma). Patent Blue V dye 0·5–1·0 ml is injected intradermally around the site of the melanoma. Immediately the groin or axilla is opened and the blue lymphatic channels are followed to the sentinel node. The node is removed and examined by both H&E and immunohistochemical staining. If the node is positive, radical lymphadenectomy is carried out. We have carried out this technique in 40 patients. In all patients sentinel nodes were identified, nine were found to have unsuspected micrometastases. In patients undergoing iliac perfusion, iliac lymph nodes were also sampled. The technique is practical and easy to master. It reliably identifies patients who may benefit from elective lymphadenectomy. If 25 per cent of patients with cutaneous malignant melanoma who are clinically stage I have nodal disease, this has great importance in the staging and treatment of the disease and for all therapeutic trials in the future. This technique of identifying the sentinel node and assessing lymphatic involvement has potential applications in breast and vulval carcinoma.

Do marker enzymes exist for malignant tumours?

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Introduction: The diagnostic value of serum enzymes in diagnosis of malignant tumours is controversial. The aim of our study was to investigate the characterization certain malignancies with serum enzyme levels.
Method: Serum enzyme activities of tumour patients prior surgery and healthy control group were measured kinetically. The activities of the investigated enzymes – alkaline phosphatase (ALP), dipeptidyl-peptidase-IV (DPP), leucine-aminopeptidase (LAP) and gamma-glutamyl transferase (GGT) were expressed in U/l. The colorectal, hepatic, gastric, renal and breast malignancies were verified histologically.
Results:

Cancer localisation	ALP U/l	DPP U/l	LAP U/l	GGT U/l
Colon	187·0±282·5	9·5±3·9	23·4±15·4	46·2±69·9
$n=39$	$P<0·05$	n.s.	n.s.	n.s.
Liver	733·2±526·9	22·3±8·9	106·5±47·8	198·9±153·7
$n=10$	$P<0·001$	$P<0·001$	$P<0·001$	$P<0·001$
Stomach	133·3±38·5	8·5±2·5	32·2±15·9	39·7±21·4
$n=9$	$P<0·01$	n.s.	n.s.	n.s.
Kidney	133·7±58·7	12·0±4·5	32·1±10·3	39·4±23·5
$n=7$	$P<0·01$	n.s.	n.s.	n.s.
Breast	148·3±21·2	10·6±2·9	29·1±12·9	35·1±9·6
$n=7$	$P<0·01$	n.s.	n.s.	n.s.
Control	73·6±52·3	8·6±5·6	22·2±15·0	31·7±30·0
$n=26$				

Increased enzyme values were detected in patients with hepatic cancer (HCC and cirrhosis!). ALP proved significant higher also in the other tumour groups. However, the average values are in normal range or were minimally increased. Changes of the serum enzyme activities were not significant seven days after surgery.

Conclusion: The examined enzymes are not perfect and specific diagnostic markers of malignant tumours. Further examinations with higher number and different groups of patients are necessary.

What can the endoscopist do for *Helicobacter pylori* positive children

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Aim: We want to draw attention to the transmission of *Helicobacter pylori* (HP) within the families.
Methods: Fifty children of HP positive parents were serologically and/or histologically investigated, and another 50 children were tested by PCR on presence of HP in their oral cavity. VacA, CagA, and UreC genes during PCR testing and Orion Diagnostics Pyloriset Latex agglutination test were used.
Results: In the first group 52 per cent of the children were serologically positive, and we found in the same group 70 per cent histologically positivity concerning the children who had upper abdominal pain. In the second group 20 per cent of the children were HP positive by PCR, and 80 per cent of the parents of these children had gastroduodenal ulcer in their history.
Conclusion: As an endoscopist when making the diagnosis of an HP infection in an adult, you should every time think of the children of those, and if there is a clinical suspicion of HP infection, the child should be clinically examined on that (supported by OTKA T-22829).

Free flap reconstruction in head and neck tumours

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Free flap reconstruction surgery with microvascular anastomosis was successfully applied in 30 cases, to extended T_4 head and neck tumours. Hereby we report on our clinical observations. In our practice the free flap reconstruction technique has not prolonged survival in a significant manner. In patient's quality of life (improved nutrition, phoniatry, restoration of earlier social relations), however, profound changes have developed.

Expression of Pepsinogen C by cutaneous malignant melanomas and correlation with clinical and histological parameters

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Introduction: Malignant melanoma of the skin (MMS) is a tumour with a rising incidence in the western countries. The more accepted prognostic factor of this tumour is the histologic evaluation of the depth of invasion according to criteria reported by Breslow and Clark. However, we need to find new prognostic markers in order to reach more clinical information with prognostic implications.

Material and methods: In order to evaluate the potential prognostic value of Pepsinogen C (Pep C) in malignant melanomas of the skin (MMS) we have studied a group of 35 patients with MMS and examined intratumoral Pep C expression using immunohistochemical methods.

Results: A total of 20 MMS (57 per cent) stained positively for Pep C. No significant association was found between Pep C expression and age of patients, histological type or tumoral localization. However, Pep C was significantly associated with sex of patients, predominant cytological type of tumours, and Breslow and Clark criteria. Thus, the percentage of Pep C positive tumours was higher in male patients with MMS (81 per cent) than in the females (36·8 per cent) (P=0·02); and so in epithelioid predominant tumours (77·7 per cent) than in fusocellular predominant tumours (33·3 per cent) (P=0·03). Similarly, the percentage of Pep C positive tumours was significantly higher in IV–V Clark tumours (83·3 per cent) than in I–III Clark tumours (25 per cent) (P<0·01), and in tumours with more than 1·5 mm depth of invasion (78 per cent), than those tumours with a depth of invasion of less than 1·5 mm (16 per cent) (P<0·01).

Conclusion: These data demonstrate the existence of a significant percentage of MMS that express Pep C. In addition, Pep C expression by MMS could represent an indicator of unfavourable outcome and tumoral aggressiveness.

Surgery in patients with haemophilia

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Surgical therapy of the patients with haemophilia is at the present time safe method due to use of a substitute antihaemophilic factor VIII, IX and recombinant factor VII. In these cases it is necessary to use surgical procedures, which minimalized a perioperative risk of the bleeding. In a cooperation with haematologist is unavoidable a substitution of the antihaemophilic factor and to achieve its optimal level.

In the years 1989–1996 we have performed 25 operations of haemophilic patients – 18 elective and seven urgent with five haemorhagic complications, two cases were treated operative, three others were treated by conservative methods. Thirty-one patients were observed due to surgical complications of haemophilia. Mortality was 0 per cent.

Conclusions: Surgical therapy of the haemophilic patient at the present time is a safe method. It requires: 1. Urgent substitution of the antihaemophilic factor and the achievement of its optimal level; 2. Only i.v. or s.c. application of the drug; 3. Don't use anticoagulants or antithrombotic drugs. 4. In emergency use of the most conservative methods. 5. The associations of elective procedure.

Splenectomy and spleen autotransplantation due to splenic cyst

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Splenectomy is known to increase the risk of overwhelming postsplenectomy infection (OPSI). There is a decrease in IgM and T-lymphocytes, primary antibody response to antigen challenge is impaired, altered opsonic function and properdin an tuftsin deficiency are noted. Autotransplantation is one of the possibilities to preserve splenic functions. The authors performed spleen autotransplantations in two cases after the splenectomy of cystigerous spleens. Ten pieces from the intact spleens, each sized 10 × 20 × 2 mm (called Furka's spleen chips) were implanted in between layers of the great omentum. The function of the reimplanted splenic tissue was demonstrated by scintigrafic investigations.

Does pneumoperitoneum during laparoscopy lead to bacterial translocation

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Aim: Although the effects of high intra-abdominal pressure on cardiac, respiratory and renal systems were evaluated in the past, there are limited numbers of studies concerning its effect on intestinal circulation. There is an uncertainty that pneumoperitoneum is leading to bacterial translocation. Our aim is to determine whether increase of intraabdominal pressure caused by carbon dioxide (CO_2) insufflation during laparoscopy leads to bacterial translocation.

Material and methods: Eighteen male dogs were used, of which seven constituted the control group (group I). Pneumoperitoneum was performed by CO_2 insufflation until intraabdominal pressure reached 15 mmHg. After 30 minutes (group II) and 120 minutes (group III) laparotomy was performed in order to investigate bacterial translocation in the samples of peritoneal smear, mesenteric lymph nodes, caecum wall, liver and spleen. Histopathological examinations were also performed.

Results: In the samples taken from the peritoneum, mesenteric lymph nodes, liver and spleen no bacterial growth was established. Bacterial colonization was significantly more in the samples taken from the caecum wall in group II (P<0·05) and group III (P<0·01) compared to the control group. Histopathological examination of the mesenteric lymph nodes showed reactive changes in group II and obvious sinus histiocytosis in group III. The changes in the mesenteric lymph nodes were the evidence of bacterial drainage.

Conclusions: More research should be conducted and emphasis should be placed on subject that intraabdominal pressure increase can cause to bacterial translocation and this could lead to multiple organ dysfunction.

Gastrointestinal stromal tumours (GIST): our surgical experience

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The gastrointestinal stromal tumours are relatively rare and their clinical behaviour at discovery is often unpredictable. In fact, besides the cases spread beyond the organ of origin and those with distant metastasis that have a clear malignant behaviour and a poor prognosis, the histological definition of their malignancy is not easy. Although the high mitotic count is usually considered the best prognostic factor, tumour and cell size, cellularity, nuclear and cellular pleomorphism, cellular atypia, nuclear hyperchromatism and tumoral necrosis are variously correlated to the behaviour of the tumour; some of these parameters are highly subjective and in their values there is considerable overlap between benign and malignant tumours so that it is not possible to utilize them as discriminating factors. For the definition of malignancy a multidisciplinary approach that combines clinical, routinary histological and immunohistochemical data is useful, but not all of these parameters can be promptly available for intraoperative diagnosis. This renders more difficult the choice of the most appropriate surgical approach that can range from a wedge resection to a partial or complete organ resection; often palliative surgery is the only possible solution. Being as lymphadenectomy in GIST does not effect survival, it is not indicated: lymphatic spread is not the primary route of metastasis. A long-term follow-up is mandatory due to the unpredictable behaviour of GIST. We present our cases of GIST indicating for each of them the surgical approach and the long-term outcome. Waiting to complete the follow-up, based on our experience, we think that while choosing the most appropriate surgical treatment must be considered an oncologic safety margin not only in highly malignant GIST but also in those cases with impredictable behaviour and that cannot be definitively assessed by intraoperative histology.

Urgent gastrointestinal surgery following vascular reconstructions

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17 119 vascular operations were carried out between 1 January 1990 – 31 December 1997 in our institute, 10 574 cases of them were reconstructive vascular surgery and 3410 interventions from them were performed due to different aorto-iliac diseases. Fifty-three urgent gastrointestinal procedures became necessary and 28 cases from them occurred either in one stage or in the same hospitalization. Vascular graft reconstruction was performed in 22 cases, but we observed graft infection only in five cases The male/female ratio was 20/8 with a mean age of 65·2 years (41–87).

The aetiological findings were as follows: a) visceral embolism in two cases; b) atherasclerotic occlusion in nine cases; c) abdominal aortic aneurysm in nine cases; d) aorto-enteric fistula in four cases; e) haemorrhage of gastric ulcer in one case; f) cancer of the stomach in one case, g) intraoperative intestinal damage in two cases.

The mortality of these operations was 35·7 per cent (10/28). The causes of the high incidence of fatal outcome were either diffuse peritonitis or cardiorespiratory insufficiency.

Conclusions: It is rarely necessary to combine the aorto-iliac reconstructive surgery with urgent gastrointestinal operations, but the mortality rate is very high in these cases This can be reason of the rare occurrence of graft infection too

Intra-operative complications during endoluminal exclusion of infra-renal aortic aneurysms

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The authors briefly present some cases with important technical problems occurred during the positioning of endoprothesis for endoluminal exclusion of infra-renal aortic aneurysms In these some patients a graft displacement occurred both proximally and distally and a re-positioning has been mandatory as well as a lengthening of one or both iliac branches in other cases. The complications have been managed with a technical cunning during the same operative session thus avoiding a conversion into an open technique, and leading to the success of the treatment

Carotid endarterectomy without angiography?

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Carotid duplex is a highly sensitive and accurate screening test, but catheter arteriography is the definitive preoperative study for carotid artery stenosis. However, its associated risks and cost have prompted the development of other imaging techniques Authors investigate if carotid endarterectomy can be done without angiography on the basis of non-invasive imaging techniques alone. Preoperative findings of duplex, CT, TCD examinations and angiography of 100 randomized patients who underwent carotid eversion endarterectomy between 1996 and 1997, have been analysed retrospectively Sensitivity, specificity, positive and negative predictive value and accuracy of the duplex vs angiography at stenosis of different grade (1–66 per cent, 67–90 per cent, 91–99 per cent, 100 per cent) have been calculated Diagnostic pitfalls and their consequences are discussed. Results show that the accuracy of duplex improves with increase of the grade of the suspected hemodynamic stenosis. Sensitivity and specificity reach 100 per cent and 97·9 per cent at the stenosis of grade 91–99 per cent. In the majority of the diagnostic pitfalls, ultrasound overestimated the grade of stenosis vs angiography. Therefore, there is a need on preoperative angiography in the case of significant, but non-critical stenoses At critical hemodynamic stenoses (91–99 per cent) it should be considered to give up angiography.

Durability of renal revascularization for preservation of renal function

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Renal artery stenosis resulting in a reduction in renal function is a major cause of chronic renal failure requiring haemodialysis. Surgery to preserve renal function in these patients can give excellent results.

The results of surgery for renal artery stenosis in 17 patients with 22 renal artery stenoses or occlusions and deteriorating renal function are reviewed The mean age was 60 years and male female ratio 8.9 Four patients were dialysis dependent and six had combined aortic and renal disease. Surgical procedures performed included aorto-renal, and iliorenal bypasses with combined aortic replacement with tube, aorto-iliac or aorto-femoral bypasses in six patients. Autogenous saphenous vein was used in 12 patients.

The mean follow-up is 60 months (range 12–120) There was no peri-operative mortality. Mean arterial blood pressure fell from a preoperative level of 191/107 mmHg, on therapy, to a current level of 142/81 mmHg ($P<0·001$). Mean serum creatinine fell from 445 µmol/l preoperatively to 250 µmol/l currently ($P<0·02$). Two dialysis dependent patients required no further dialysis following surgery Medication fell in both dosage and number of agents from a mean of 2·3 agents pre-op to a current level of 1·6 ($P<0·05$) Renal function was maintained or improved for the duration of follow-up in all but two patients. Nine patients are still alive. One patient required further dialysis five years following surgery and renal function deteriorated two years post surgery in one patient.

It is concluded that renal artery surgery for preservation of renal function is a worthwhile procedure in patients with renal artery stenosis and deteriorating renal function

Iliac Wallstents and endovascular repair of abdominal aortic aneurysms (AAA): a useful combination?

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Aims: Iliac arterial tortuosity and luminal narrowing can cause problems during insertion of bifurcated aortic stent grafts with possible limb occlusion We aimed to review the effect of prophylactic iliac stenting on the outcome of AAA stent grafts and associated radiological exposure.

Methods: During a 22 month period, 40 patients underwent endovascular treatment of infra-renal AAAs. In all cases a bifurcated device was successfully deployed Nine patients were noted to have an iliac stenosis or narrowing with significant tortuosity Wallstents were placed in the iliac vessels of all nine patients (seven unilateral, two bilateral) prior to insertion of the aortic stent Follow-up was by CT scan at 1, 3, 6, 12, 18 months (median six; range 1–21 months)

Results:

	Wallstent	No Wallstent	*P*
Number	9	27	
Median fluoroscopy time	27 mins	32 mins	n s
Median contrast volume used	350 mls	290 mls	n s

Two early and two late iliac limb occlusions have occurred, none on the group pre-treated with Wallstents. One early occlusion occurred during treatment of a proximal endoleak. The remaining three have all been associated with significant iliac angulation (>80°) There were no procedural deaths or conversion to open repair. One patient pre-treated with a Wallstent died on day six from a myocardial infarct. Of the remaining eight patients, all have patent iliacs bilaterally, no endoleaks and no distal complications. Overall 30 day mortality = 5 per cent (11·1 per cent for the Wallstent group).

Conclusion: A high proportion of bifurcated stent grafts will occlude at least one limb in the presence of iliac tortuosity or stenosis. Wallstents appear to decrease this occlusion rate without significantly increasing radiological time, allowing easier stent graft deployment.

Direct analysis of free radical release during aortic aneurysm repair by electron resonance

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Aims: Reactive free radical species (ROS) generated during abdominal aortic aneurysm (AAA) surgery have been implicated in the resulting ischaemia–reperfusion injury. Our aim was to determine the applicability of Electron Spin Resonance (ESR) spectroscopy for analysis of ROS produced during AAA repair.

Methods: Using a femoral line, 1 ml blood samples were obtained from six patients undergoing open AAA repair. These were immediately mixed with 0·5 ml of α-phenyl-N-tert-butyl nitrone (PBN, 50 mM in 0·15 M NaCl) spin trapping agent, and the mixture frozen in liquid nitrogen. After thawing, vortex mixing with 0·5 ml toluene and centrifuging at 10 000 g, the clear supernatant was flame sealed in a glass capillary tube for analysis via ESR spectroscopy. The height of the central peak of the triplet PBN-adduct spectrum is proportional to the ROS content of the sample allowing comparison.

Results:

Sample		Free radical content (arbitrary units) [mean ± SD]	
Pre-clamping		230±100·14	
Post-clamping:	10 min	506±170	$P<0\cdot03$
	1 hour	229±84·87	$P>0\cdot4$ (ns)
	4 hours	419·111·05	$P<0\cdot04$
	24 hours	534±177·9	$P<0\cdot05$

Conclusion: This technique identifies two significant peaks in the free radical content of venous effluent from tissues undergoing ischaemic–reperfusion during open AAA repair. With refinement it could help in the development of methods to modulate the associated injury.

Change in aneurysm diameter following aortic stenting: is it a measure of success?

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Aims: If abdominal aortic aneurysms (AAA) fail to decrease, or actually increase in size following stenting, there may still be a risk of rupture. Our aim was to examine early changes in AAA size following apparently successful aortic stenting.

Methods: Forty AAAs have been repaired using a bifurcate system. The maximum aortic diameter was recorded for each patient on a preoperative CT scan. Follow-up scans have been performed at regular postoperative intervals (0, 1, 3, 6, 12 + 18 months). All scans have been examined for endoleak and change in AAA diameter by a consultant interventional radiologist. Patients have been grouped dependant upon intitial AAA size (Group 1: 45–54 mm; Group 2: 55–64 mm; Group 3: >65 mm).

Results: Two patients died prior to discharge. Thirty-three patients have reached one month follow-up (median six months; range 1–21 months). Changes in AAA diameter are shown as percentage of the immediate postoperative measurement (giving median values and ranges).

	Group 1	Group 2	Group 3
Number of patients	11	14	8
Median FU (months)	6	6	6
% diameter change	–4·3 (–28·8 to +1·5)	–2·4 (–30 to +8·3)	–2·4 (–15·6 to +4)

Since stent insertion 20 aneurysms have decreased, seven increased and six remained unchanged in size. Two patients have increased by greater than 5 per cent and neither have an endoleak evident on CT.

Conclusion: Despite an apparently successful procedure CT scanning has revealed shrinkage of the sac in only 60·6 per cent of patients and AAA diameter has actually increased in 21·2 per cent. These patients may have small endoleaks undetected on CT and interpretation of 'stenting success' should be guarded until long-term results are available.

Postural effect on lower limb arterial calf inflow in health and peripheral vascular disease

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Aims: To comparatively evaluate the effect of postural alteration on lower limb arterial flow velocity haemodynamics a) in healthy subjects and b) in patients with intermittent claudication (IC) (Fontaine II) due to peripheral vascular disease (PVD).

Material and methods: The postural effect was evaluated in 37 limbs of healthy subjects (Group 1) and 50 limbs of patients with IC (Group 2, ABI range 0·39–0·76; median 0·57) using duplex U/S (HP Sonos 2500). All patients in group 2 had superficial femoral artery (SFA) disease. Flow haemodynamics (mean and SD) [volume flow (Q) (ml/min), mean velocity (MV), peak systolic (PSV), end diastolic (EDV) velocities (cm/s) and pulsatility index (PI)] were measured in the lying (L) and sitting (S) positions.

Results:

Group 1	MV	PSV	EDV	PI	Q
Lying	8·8 (12–5)*	54 (66–41)*†	4·7 (6–4)*	6 (8–4)†	111 (154–68)*
Sitting	4·5 (6–3)	37 (46–28)†	3·4 (4–3)	9 (11–6)*†	57 (83–30)
Group 2					
Lying	12·5 (17–8)*†	29 (42–16)*	5·8 (8–4)*	2 (3–1)	113 (166–61)*
Sitting	8·4 (12–5)†	23 (33–13)	4 (6–3)†	2·5 (4–1)*	76 (116–35)†

*: $P<0\cdot01$ Intragroup (L vs S) (Wilcoxon SR).
†: $P<0\cdot01$ Intergroup (L vs L) (S vs S) (Mann Whitney).

Conclusions: Lower limb arterial Q and flow velocities decrease significantly when posture is altered from lying to sitting both in normal subjects and claudicants. This and increase of PI on sitting indicate enhancement of arterial resistance to flow secondary to peripheral vasoconstriction. The orthostatic response in claudicants is significantly attenuated reflecting a marked derangement in the quality of the veno-arteriolar reflex. Understanding these postural changes is a key to the development of therapeutic measures to improve flow and collateral circulation. Mechanical means, such as impulse devices, by reducing peripheral resistance to flow on sitting, have shown promising results in the treatment of intermittent claudication.

Duration of arterial calf inflow enhancement with Intermittent Pneumatic Compression of the calf

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Recent data indicate that Intermittent Pneumatic Compression (IPC) applied daily (2–3 hours) can significantly improve the haemodynamics and walking ability of patients with Intermittent Claudication (IC) due to PVD. Delivery of a pneumatic impulse to the leg expels the venous blood

up to the thigh and enhances shear stress in the vessel walls, causing increase of the arteriovenous gradient and release of endothelium dependent relaxing factors that attenuate peripheral resistance and increase arterial flow.
Aim: To determine the flow velocity changes that occur in the arterial calf inflow when the leg is subjected to a pneumatic impulse in healthy subjects and patients with IC.
Material and methods: Twenty-four normal limbs (N) and 26 limbs with PVD (IC) matched for age, sex and risk factors. All PVD legs examined had a patent popliteal artery and a severely diseased superficial femoral artery. Arterial calf inflow haemodynamics [volume flow (Q ml/min), the mean (MV), peak systolic (PSV) and end diastolic (EDV) velocities (cm/s), and pulsatility index (PI)] were obtained in the popliteal artery using Duplex U/S after a 20 minute rest. Measurements were obtained at rest and during the application of IPC in the calf, through to 50 seconds after the delivery of the impulse (140 mmHg, 4 sec). Data were analysed at rest (0) and 5, 15, 25, 35, 45 and 50 sec from the cessation of impulse.
Results:

		0s	5s	15s	25s	35s	45s	50s
Q	N	49	179*	120*	88*	60*	49	49
	IC	55	163*	92*	77*	71*	65*	64*
MV	N	4†	15*†	10*†	8*†	5*†	4†	4†
	IC	8·4	21*	15*	2·5*	11*	9·4*	9*
PSV	N	39·2†	56*†	46*†	44·5*†	41·6*†	39·2†	39·15†
	IC	22·1	41·9*	32·8*	30·5*	28·1*	24·3	24·3
EDV	N	3·4	9·2*	5·6*	4·1*	3·7	3·4	3·4
	IC	3·8	11·7*	7·2*	5·2*	4·1*	3·9	4·28
PI	N	9·3†	3*†	4·5*†	4·9*†	7·1†	8·8†	9·3†
	IC	2·3	1·47*	1·73*	2·02*	2·36*	2·27	2·35

*: $P<0·01$ intragroup comparison (Wilcoxon ST).
†: $P<0·01$ intergroup comparison (Mann–Whitney).

Conclusions: Arterial calf inflow velocity augmentation achieved on application of IPC is a phenomenon lasting up to 35 seconds in healthy subjects and more than 50 seconds in patients with IC due to PVD. Three phases can be demonstrated, an early one characterized by maximal levels of flow velocities and minimal PI, a middle phase where flow velocities are markedly attenuated, and a final one representing an asymptotic slow return to baseline. Flow enhancement with IPC is associated with a significant increase of EDV and attenuation of PI, indicating that the involved mechanisms act by reducing peripheral resistance to arterial flow.

The surgical treatment of the extremity vascular injuries

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The frequency of the vascular trauma in the civilian life has increased significantly in the past decade in Hungary. This is due to more automobile and industrial accidents, the appalling increase in gunshot and stab wounds and the increasing use of therapeutic and diagnostic techniques involving the cannulation of major blood vessels. The consequences of the vascular trauma – like haemorrhage and ischaemia – threaten the patient's life.

During the period 1986–1997, 81 civilians with 100 vascular injuries were treated. Eighty-five primary repairs and 15 late operations for traumatic false aneurysms and arteriovenous fistulas were performed. Penetrating trauma occurred in 55, gunshot in 13 and blunt in 18 of patients. Fourteen indirect injuries like hyperextension, deceleration and arteriospasm were encountered. Nearly 80 per cent of injuries were located on the extremities; 35 isolated vascular and 46 multiple traumas were treated. Concomittant bone in 20, peripheral nerve in 18, cerebral in seven and abdominal or thoracic organ injuries were observed in 10 patients. Stable patients underwent complete vascular evaluation including arteriography. The haemodynamically unstable patients were brought directly to the operating room. Preoperative arteriography was needed in 20 of 90 arterial injuries. Vascular injuries were amenable to repair by means of lateral suture or using autologous vein or PTFE grafts.

The correct diagnosis of the vascular trauma, the minimalized duration of ischaemia by appropriate cooperation in planning repair procedures between orthopaedics and vascular surgeons are the most important factors of the surgical treatment.

Renal artery stenosis: the significance of its incidental finding on peripheral angiography

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Aims: As more angiograms are being performed for lower limb ischaemia RAS is increasingly diagnosed as an incidental finding. We aimed to determine the prevalence of RAS in patients with peripheral vascular disease and its impact on patient outcome.
Methods: All peripheral angiograms performed over a two year period were independently reviewed to determine the degree of RAS. Those patients found to have RAS of 50 per cent or more were then studied further. Mortality risk factors were recorded and statistical analysis performed using χ^2-squared tables with Yates' correction. Follow-up was available for a minimum of two years and a maximum of four years.
Results: Analysis of 1102 consecutive angiograms revealed 156 (14·2 per cent) patients with RAS. In this group there was a high overall mortality rate of 21·2 per cent, hypertension and diabetes were common, 62·7 per cent and 20·6 per cent respectively, whilst elevated serum creatinine >130 µmol/l was found in 10·9 per cent. Bilateral or severe unilateral stenosis >90 per cent was identified in 43·6 per cent. However, the only risk factor useful in identifying a high mortality sub-group was elevated baseline creatinine (P=0·004, two-tailed t-test).
Conclusion: We conclude that the prevalence of RAS merits flush aortography to visualize the renal arteries in all patients undergoing peripheral angiography. Furthermore, any patient with pre-existing elevation of creatinine and RAS is at exceptionally high-risk and merits urgent investigation of renal and cardiac function.

Non-invasive evaluation of the effect of posture on lower limb arterial blood flow in patients with claudication

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Aims: To determine the influence of posture on the arterial blood flow in the lower limbs in patients with and without peripheral arterial vascular disease.
Material and methods: A consecutive series of 22 patients (31 limbs) with chronic intermittent claudication short of rest pain were studied. Patients were scanned using 5·5–7·5 MHz high resolution line scan head probe. The popliteal artery blood flow and pulsatility index were calculated from the Doppler spectral waveform. These measurements were taken in horizontal as well as in sitting position. Eight normal individuals with matched age and sex (16 limbs) were recruited and the same measurements were repeated (control group).
Results: In the control group the mean popliteal blood flow in the horizontal position (102·9±41·5) ml/min was significantly higher (P=0·0039) than in the sitting position (62·5±38·7) ml/min. However, in claudicant group the mean popliteal blood flow in the horizontal position (96·1±57·3) ml/min was not significantly higher (P=0·0809) than in the sitting position (69·9±45·8) ml/min. The change in posture has produced a significant change (P=0·0226) in the pulsatility index in the control group from the sitting position (10·50±7·88) to the horizontal position (4·97±3·79). However, the change in posture has produced a non significant change (P=0·8470) in the pulsatility index in the claudicant group from the sitting position (2·919±2·40) to the horizontal position (3·070±2·97).
Conclusion: The results indicate that posture plays an important role in the haemodynamic arterial blood flow changes. This might have an implication in rehabilitation of patients with chronic leg ischaemia.

High resolution ultrasound prior to endarterectomy: the accuracy of grading ICA stenosis

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Aim: The aim of this study was to evaluate the accuracy of ultrasonic B-mode images of ICA in estimating the degree of stenosis.

Material and methods: In a random consecutive series of patients scheduled for CEA routine duplex scanning was performed using ATL HDI 3000 and 7–4 MHz probe. Good quality images in B-mode (both in longitudinal and transverse views) were frozen on the screen. The percentage diameter and area reduction were calculated from each view respectively. Peak systolic (PSV) and end diastolic velocities (EDV) were measured at the proximal CCA and ICA within the jet of turbulence. The following velocity ratios were used to calculate the degree of haemodynamic stenosis (PSVic/PSVcc). (EDVic/EDVcc) and (PSVic/EDVcc). Endarterectomy specimens of the same patients were scanned immediately in a mixture of saline and gel media. The site of maximal stenosis was marked and 0·2 mm transverse pathological blocks were obtained. The duplex measurements were compared to the percentage area and diameter reduction from transverse sections of the specimens. A millimetre scale was placed next to the specimens which was captured by video. The area reduction was measured by playing the video and using the same duplex setting as above.

Results: The following table summarizes the difference in the estimated diameter stenosis using different methods in relation to that estimated from endarterectomy transverse blocks (as a gold standard). Twenty-nine out of 32 were in the region of 70–99 per cent.

Duplex method used	Percentage of cases with concordant stenosis to that estimated from the surgical specimens	Percentage of cases with disconcordant stenosis relative to that estimated from the surgical specimens
B-mode images	93%	6%
PSVica	79%	21%
EDVica	24%	76%
PSVica/PSVcca	76%	24%
EDVica/EDVcca	60%	40%
PSVica/EDVcca	76%	24%

Conclusion: The results indicate that images obtained with B-mode are the most accurate in determining the degree of stenosis. Diameter and area reduction (measured on duplex) might be more appropriate parameters to be used in studies that evaluate the sensitivity and specificity of ultrasound with angiography as gold standard.

Graft dilatation following abdominal aortic aneurysm resection and grafting

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Dilatation of aortic prosthesis following abdominal aneurysm surgery has been documented with both knitted and woven dacron grafts.

Aim: To review the experience in a single institution with both types of grafts, and to evaluate both rate and degree of dilatation, and association of dilatation with graft-related complications.

Material and methods: Between January 1987 and December 1992, elective repair of abdominal aortic aneurysm was undertaken in 219 patients. Of these patients, 146 had at least one follow-up ultrasound scan to evaluate their graft. These patients were analysed with respect to age, sex, size of initial aneurysm, type of graft, size of graft used, time of follow-up and diameter of graft at follow-up scan. Any complications referable to the graft or recurrent disease was also documented at this time.

Results: A total of 216 scans were available for analysis. There were 123 male patients and 23 female patients in the group. The mean age was 72 years, and the mean preoperative aneurysm size was 5·8 cm. Thirty-four patients had a woven dacron graft inserted, while 112 were grafted with a knitted dacron prosthesis. Mean percentage increase in size for woven dacron was 17·3 per cent, while that for knitted dacron was 38·9 per cent ($P<0{\cdot}0001$). Further analysis of the scans showed that the majority of dilatation occurred early, and the grafts were then relatively stable. No specific complications related to graft or anastamotic dilatation were noted.

Conclusions: Dilatation following implantation is a well known phenomenon affecting dacron, particularly in a knitted configuration. Some authors have suggested that graft dilatation is either an inherent failure mode of the material, or a precursor of more significant complications. This study contradicts this view, and dilatation was not associated with any adverse outcome. However, graft complications are known to be related to the weight of graft inserted, particularly in knitted grafts, and there is some question as to the dimensional stability in vivo of ultralightweight grafts. This raises concerns as to the behaviour of grafts inserted during endoluminal repairs and the possibility of late dilatation.

Duplex detected stenoses in angiographically normal vein grafts: is angiography still the gold standard?

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Aim: To review the sensitivity of duplex scanning and angiography at detecting vein graft stenoses in patients on a graft surveillance programme.

Patients and methods: Since February 1993, 143 patients with 148 vein grafts (70 per cent in situ, 30 per cent reversed) have been included in a prospective, open, non-randomized study, attending postoperative infrainguinal vein graft surveillance for a minimum of six weeks, 57 graft stenoses in 57 grafts were identified by duplex scanning as a localized high velocity jet. Angiography was performed in all except 12 patients.

Results: Angiography confirmed vein graft stenoses in all but 10 patients. Of these, five patients remain stable and asymptomatic with a persisting duplex abnormality. The remaining five patients, although asymptomatic, exhibited disease progression on duplex and surgical intervention confirmed significant stenoses which were successfully treated.

Conclusion: The results suggest that duplex scanning is a reliable imaging modality for detecting vein graft stenoses. Selection for surgical correction can be made, in some circumstances on the basis of clinical and ultrasound criteria alone.

Management of patients with failed endovascular stents?

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Percutaneous transluminal angioplasty (PTA) with endovascular stenting is now commonly used in the treatment of aortoiliac occlusive disease. There is limited data on the long-term outcome of patients in whom stenting fails. We have carried out a retrospective analysis of all patients who underwent stenting whom the treatment failed. Between July 1993 and July 1996, a total of 80 patients had iliac stents inserted. In 19 patients the stenting failed. There were 14 females and five males with a mean age of 55 years (range 35–92). Fifteen presented with intermittent claudication and four with rest pain. All patients had aortoiliac occlusive disease which was demonstrated on arteriography to be suitable for PTA. Six patients had Palmaz 294 stents, seven patients had kissing Palmaz 394 stents and six had wall stents. In eight patients the stents blocked immediately, but radiological salvage was possible only in four with good symptomatic outcome. In the other four patients, arterial reconstructive surgery was performed. Only one patient had a successful outcome and three patients eventually came to amputation of the lower limb. In 11 patients the stents blocked between one month and four years. In two patients radiological salvage was attempted but failed and arterial bypass surgery was performed which was successful in one patient. Of the remaining nine patients who underwent arterial reconstructive surgery, six remain symptom free and three still have claudication. Though stenting of iliac disease is widespread, our experience suggests that complications are not uncommon. Surgery, rather than further radiological intervention is usually needed.

Coexisting abdominal aortic aneurysm and intra-abdominal malignancy: which lesion to treat first?

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Background: The management of simultaneously occurring abdominal aortic aneurysm and intra-abdominal malignancy is controversial. It is unclear whether to resect the aneurysm first or the malignancy or both simultaneously. If the malignancy is resected first there is a risk of post-operative rupture of the aneurysm. If a simultaneous resection is performed there is a risk of prosthetic graft infection from contamination by gastrointestinal or urinary tract contents.

Method: All relevant papers derived from medline and manual searching were reviewed and analysed.

Results and conclusions: The literature supports the conclusion that the lesion of greatest priority is that posing the greatest threat to the patient, and that this is usually the aneurysm, especially if over 6 cm in size. For renal malignancies simultaneous resection is the treatment of choice, but for bladder cancer the best management is unclear. Aneurysms should usually be resected in preference to colorectal cancer unless the cancer is perforated or obstructed. If both lesions are complicated there is a case for simultaneous resection.

Femoro-femoral bypass

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Aim: This is a prospective study of 75 patients who had a femoro-femoral crossover graft. The study was designed to ascertain the value and limitation of this extra-anatomical graft.

Material and methods: Seventy-five patients had this bypass for disabling claudication (24), rest pain (24) or gangrene (27) at one unit between November 1986 and October 1995. In all patients an 8 mm Dacron graft was placed behind rectus abdominus muscle. All patients had pre- and postoperative Doppler pressure studies and peroperative pressure measurements. All patients have been followed up for a minimum of two years. Data have been analysed by Student's t-test and significance assessed as $P<0{\cdot}05$.

Results: There were three deaths in the first 30 days and 17 further deaths between six months and five years. The graft significantly increased Doppler ankle pressure.

	Brachial	Ankle
Preoperative	158	57
Postoperative	139	103 * $P<0{\cdot}05$

The patency was 80 per cent at 12 months and 68 per cent at 5 years. Eight patients developed severe ischaemia or stealing of the donor limb. This was due to (1) intimal hyperplasia, (2) existing occlusion of donor superficial femoral artery, (3) the development of stenosis of the donor iliac artery.

Conclusion: A femoro-femoral crossover graft is a successful graft with good long term patency. However, a steal phenomena may occur on the donor side and those at particular risk can now be recognized preoperatively and precautions taken.

Objective mobility assessment in peripheral vascular disease and treatment by angioplasty

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Aim: To objectively measure activity differences in the home environment between patients with peripheral vascular disease (PVD) and controls, and demonstrate whether treatment by percutaneous transluminal angioplasty (PTA) improves mobility.

Methods: Twenty claudicants and 13 controls without PVD were studied. Using NUMACT (a modified Psion$^{\mathrm{TM}}$ with two position sensors and accelerometer) postural changes (standing, sitting, lying) and activity (number and amplitude of steps) were recorded in real time for 24-hour periods. Energy was calculated as step number × amplitude (arbitrary units). Ischaemia was measured using ankle brachial pressure index (ABPI). Twelve claudiants underwent PTA and the measurements repeated two weeks later.

Results: Median standing/walking time was 186 minutes in claudicants compared with 371 minutes in controls ($P<0{\cdot}01$). Median number of steps taken was 7088 in claudicants compared with 14 216 in controls ($P<0{\cdot}01$). Median energy expenditure was 172 761 in claudicants compared with 472 505 in controls ($P<0{\cdot}01$).

In eight cases ABPI improved by $\geq 0{\cdot}15$ after PTA, in four by $<0{\cdot}15$. Cases demonstrating haemodynamic improvement showed increased standing time of 99 minutes (median) $P=0{\cdot}02$, increased number of steps by 3517 (median) $P=0{\cdot}02$ and increased energy expenditure of 135 731 (median) $P=0{\cdot}04$.

Conclusion: These data demonstrate impaired mobility in claudicants, which is improved by haemodynamically successful PTA. This has not been objectively measured before.

Selective shunting using transcranial Doppler, near infrared spectroscopy and stump pressure measurements during carotid endarterectomy

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Aims: Near infrared spectroscopy (NIRS) and transcranial Doppler (TCD) monitoring can be used during carotid endarterectomy (CEA) to monitor cerebral perfusion. This study aims to compare the usefulness of NIRS, TCD and carotid stump pressure measurements in selective shunting during CEA.

Method: Thirty-five patients undergoing CEA under general anaesthetic had ipsilateral cerebral oximetry and TCD monitoring of the middle cerebral artery (MCA). After carotid clamping, the mean carotid stump pressure, the fall in MCA velocity and cerebral oxygen saturation were measured.

Results: Patients were divided into those with a stump pressure >50 mmHg (18) or ≤50 mmHg (12). The median fall in MCA velocity when the stump pressure was >50 mmHg was 31 per cent compared to 51 per cent when the stump pressure was ≤50 mmHg. There was a significantly larger fall in MCA velocity when stump pressure was ≤50 mmHg ($P=0{\cdot}01$, Mann–Whitney U). The fall in MCA velocity inversely correlated with the ratio of stump pressure to mean arterial pressure (Spearman $r=0{\cdot}73$ 95 per cent CI: 0·87 to 0·48, $P<0{\cdot}0001$).

The fall in cerebral oxygen saturation was not associated with mean stump pressure ($P=0{\cdot}2$). The fall in oxygen saturation was inversely correlated with the ratio of stump pressure to mean arterial pressure (Spearman $r=0{\cdot}55$ 95 per cent CI: 0·83 to 0·06, $P=0{\cdot}03$). There were no postoperative neurological events in the study.

Conclusions: The measurement of MCA velocity by TCD may be a useful adjunct to stump pressure measurement in deciding when to use a shunt as well as for shunt monitoring. Cerebral oxygen saturation may not be as comparable, casting doubt on its usefulness in clinical practice.

Assessment of fistulography for surgery of angioaccess for haemodialysis

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The aim of this study was to evaluate the reliability of fistulogaphy of arterio-venous fistula for chronic haemodialysis.

Material and methods: Contrast medium was injected via needle inserted in arterial part of the fistula. The image intensifier was centred on the fistula and the draining veins as far as the subclavian vein subsequently. Total of 67 procedures was performed on 48 patients presenting with native a-v fistulas for haemodialysis on the upper extremities.

Results: Fistulography demonstrated following abnormalities: venous stricture 13 cases; venous aneurysm five cases; multiple venous collaterals two cases; central venous occlusion three cases. No complications related to injection, contrast dose were noted. Performed procedures resulted in 17 cases of surgery and five percutaneous transluminal angioplasty including two vascular stenting.

Conclusions: 1. Fistulography a-v shunt is a simple, safe and easy procedure. 2. Fistulography proved to be of excellent use in constructive and reconstructive surgeries of fistula and prevent early complications caused by inadequate vein draining.

Clinical correlates of embolic events on transcranial Doppler

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Aim: It was to establish the relationship between the ipsilateral embolic count (EC) in the middle cerebral artery (MCA) on transcranial Doppler (TCD), carotid plaque echodensity, ipsilateral cerebrovascular symptoms (CVS) and ipsilateral cerebral CT infarctions (CCTI).

Methods: Fifty-nine patients with 80 carotid plaques; 26 symptomatic and 54 asymptomatic, having stenosis on Duplex from 50–99 per cent were studied. The ultrasonic images of carotid plaques were normalized in a computer using two echoic reference points: the GSM (grey scale median) of the blood and the GSM of adventitia. GSM represents the median of the frequency distribution of tones in selected areas of the image. Normalization is a linear scaling (0–255 grey tones) which transforms all images so that the GSM of the blood to become 0–5 and the GSM of the adventitia to become 180–200. The GSM of the normalized image of the plaques was used as a measure of plaque echodensity. The ipsilateral MCAs were monitored on TCD for 30 minutes for the EC and the presence of ipsilateral CVS and ipsilateral CCTI were noted. Haemodynamic and lacunar infarctions were excluded since these do not have an embolic basis.

Results: The prevalence of embologenic plaques (EC>2) was higher in the echolucent (GSM<30) than in the echogenic (GSM>30) plaque population [48 per cent (20/42) – 26 per cent (10/38)] symptomatic than asymptomatic plaque population [54 per cent (14/26) – 30 per cent (16/54)] and CT infarction than CT infarction free plaque population [64 per cent (9/14) – 32 per cent (21/66)] (χ^2, $P<0{\cdot}05$).

Conclusion: These results establish the relationship between the EC, GSM, CCTI and CVS, indicating that EC can be used to identify unstable carotid plaques and suggesting their possible application in natural history studies of carotid plaques.

The progressive inflammation of peripheral vascular disease: a cause for concern?

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Introduction: Patients with PVD (Peripheral Vascular Disease) are advised to walk to their maximum claudication pain to help improve walking distance. However, each episode of claudication pain is associated with a short-lived ischaemic episode followed by one of reperfusion. This may result in an injurious systemic inflammatory response that becomes perpetuated with vascular disease progression.

Aim: To assess the inflammatory response of simple exercise, of claudication, and of increasing category of PVD in terms of the markers of ischaemia reperfusion type injury.

Methods: Seventy-five patients were enrolled in this experimental study. Data were collected from 22 patients with grade 0 claudication (controls), 28 patients with grade 1 claudication, and 25 patients with grade 2 claudication (SVS/ISCVS [Society for Vascular Surgery/International Society for Cardiovascular Surgery] classification). Levels of plasma neutrophil elastase, total antioxidant capacity (TAC), the urine albumin to creatinine ratio (UACR), and neutrophil CD11b expression were determined after rest. The claudicants and control groups then underwent standardized treadmill exercise, after which the above markers were re-measured at 5, 30 and 60 minutes from the test.

Statistics: Data are treated as non-parametric. The Mann–Whitney *U* test is used for inter-group comparison.

Results: There was no significant difference in resting TAC between the three groups. Grade 2 claudicants had significantly higher baseline urine albumin leak ($P<0{\cdot}01$), and CD11b expression ($P<0{\cdot}01$), compared to the control group and grade 1 claudicants. Exercise caused significant increases in neutrophil CD11b ($P<0{\cdot}01$), and neutrophil elastase ($P<0{\cdot}01$), that were not seen in controls.

Resting measurements of inflammatory markers according to category of PVD

Category of PVD	Number	TAC	Neutrophil CD11b Mean channel fluorescence	UACR mg/mmol
Grade 0	22	720 (630–858)	2·53 (2·17–3·2)	0·49 (0–1·3)
Grade 1	28	813 (636–909)	3·08 (2·38–3·9)*	1·96 (0·86–3)*
Grade 2	25	765 (400–980)	11·5 (7·3–15·2)†	6·4 (1–7·5)†

*$P<0{\cdot}05$ Mann–Whitney U test vs control group.
†$P<0{\cdot}01$ Mann–Whitney U test vs control group.

Conclusion: Increasing severity of PVD is associated with systemic inflammatory changes. These changes are also seen episodically in claudicants during exercise, and may contribute to the progression of their vascular disease.

Polymorphism of apolipoprotein E genotype in patients with iliofemoral and femoropopliteal reconstruction followed by restenosis

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The risk factors in restenosis after peripheral vascular reconstructions are very different including technical errors, neointimal proliferation, thrombotic factors, haemorrheological components, diabetes, hypertension, renal diseases and smoking.

The aim of this study was to investigate the genetic alterations of apolipoprotein E, which is a main determinant of lipoprotein metabolism under physiological and pathophysiological conditions, respectively.

A group of 107 patients (70 male and 37 female, aged 39–78 years) with severe peripheral vascular atherosclerosis and early (within 6 months) or late (after 12 months) restenosis after vascular reconstruction were examined. Blood was taken after 12 h fasting in supine position for determination by enzymatic method of serum cholesterol and triglycerides, determination by precipitation technique of HDL-cholesterol, and for immunological detection of apolipoproteins. Leukocyte DNA was prepared for the detection of apolipoprotein E genotypes and F4 and F5 primers were used to PCR amplification followed by HhaI enzymatic digestion and gelelectrophoresis. Blood donors (n=253) served as controls.

Significantly elevated serum cholesterol [6·4 (1·3) vs 5·5 (1·1) mmol/L, P=0·0001] and serum triglyceride [2·2 (1·7) vs 1·5 (0·8) mmol/L,

P=0·0001] level was found in the patients compared to controls. There was no difference in HDL-cholesterol level between the two groups [1·1 (0·62) vs 1·0 (0·3) mmol/L, P=0·1]. A preponderance of apolipoprotein E 3/4 (26/107 24·5 per cent vs 37/253 14·6 per cent, P=0·02, Fisher's Exact Test) was detected in the whole atherosclerotic group with restenosis compared to control population. In patients with early restenosis compared to those with late restenosis, no difference in the distribution of apolipoprotein E genotypes was found.

In conclusion, besides lipoprotein lipids and other metabolic components, apolipoprotein E 3/4 may play a pivotal role as risk factor for restenosis in peripheral vascular atherosclerotic disease.

Endoscopic venous surgery for incompetent perforators

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A pilot study assessing the efficacy of subfascial endoscopic ligation of incompetent venous perforators in 20 patients was undertaken.

Patients and methods: There were 15 females and five males with an average age of 68 and 52 years respectively. The indications for surgery were lipodermatosclerosis in 16, eczema in 11 and non-healing ulcers in six patients. All patients had incompetent venous perforators diagnosed with colour flow Duplex Doppler and phlebography. The operation was carried out through a single port using the Olympus SEPS system in an avascular field under a tourniquet. The average operating time was 45 minutes. Seven patients had adequate superficial venous surgery previously whereas 11 had conjunctional superficial venous surgery with SEPS. One patient had no associated junctional venous incompetence.

Results: The operation was successfully carried out in all but one patient. There were 22 legs and 29 sites in 19 patients. Incompetent perforators were found in 21 medial and eight lateral sites: 1–3 perforators ligated in 18, 3–5 perforators in six and 5–7 perforators in five sites. Active lipodermatosclerosis improved in 15/17 patients and venous ulcers healed in 4/6 patients. Skin eczema and aches/pains were cured in all. The average hospital stay was 2·6 days. Early complications occurred in three patients; haematoma in one and wound infection in two. All three patients having recurrent skin problems had significant missed perforators which were ligated in the second sitting.

Conclusions: This study has shown that subfascial endoscopic ligation of venous perforators can be performed effectively with a low incidence of complications. There is, however, a learning curve as all three patients with missing perforators were in the first half of the study.

Is determination of the lowest level of amputation with transcutaneous oxygen better than empiric estimation?

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In our study we evaluated patients before leg amputation. The patients were divided in two groups: group 1 (382 patients) – the amputation level was estimated by empiric experiences; and group 2 (59 patients) – the amputation level was estimated by measuring of transcutaneous oxygen ($PtcO_2$). In group 2 we followed importance of Doppler examination (ankle-brachial pressure index, ABPI), palpable pulse near the amputation level, regional perfusion index (RPI) and transcutaneous oxygen ($PtcO_2$). We evaluated the importance of haemoglobin and albumin as predictive factors of stump healing in both groups.

In empiric group (382 patients) the number of reamputations was 84 patients (22 per cent) and in oxymetric group the number of reamputation was four patients (7 per cent) – three times lower and with statistical significance. Comparing of sensitivity, specificity and effectivity of ABI, palpable pulse, RPI and $PtcO_2$ we found out that the most important value for estimating propriate amputation level has RPI and $PtcO_2$. Critical value of $PtcO_2$ is 28 torr.

The level of albumin (Alb >40 g/l) has statistical significance and we can consider it as a predictive value of stump healing. The patients with this value of albumin before amputation had four times lower number of reamputations. We did not find out statistical significance in haemoglobin.

Conclusions: 1. The most probable healing of the stump is in the vicinity of palpable pulsation. 2. The most probability of stump healing have patients with Alb >40 g/l. 3. Healing of the below knee stump has the highest probability at ABI >0·45. 4. Critical value for practically complete stump healing is for $PtcO_2$ >28 torr as well as RPI >0·6 immediately above the level of amputation.

Patients referred from national centres to a single centre for consideration for endovascular abdominal aortic aneurysm repair: reasons for referral and rejection

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Aims: The referral pattern of patients with abdominal aortic aneurysms (AAA) to a single centre has changed following the introduction of endovascular repair (EVR) of AAA. We aim to show this change and the reason for referral and rejection for EVR of AAA.

Method: A retrospective study of all elective referrals of patients with AAA to a single centre over a three year period.

Results: Three hundred and sixty five patients were referred over the study period. The proportion referred from national centres for EVR increased over the study period. One hundred and ten patients were referred from national centres. The commonest reason for referral was that the patient was at high risk at open repair due to ischaemic heart disease (n=37). Of the 110 patients, 63 subsequently underwent EVR of whom 54 are still alive after a median follow-up of 11·8 months. The reasons for rejection for EVR are divided into anatomical and others. The commonest anatomical reason for rejection was that the proximal neck was too short (n=8) and in the other group, the commonest reason for rejection was that the patient was unfit for a general anaesthetic (n=3). Of those rejected (n=47), 10 have undergone open procedure in their referring hospital and 33 have not had any surgery.

Conclusion: There has been an increase in the number of referrals of patients with AAA from national centres although not all are suitable for EVR.

A prospective, double-blind, placebo-controlled crossover study to assess the effect of sublingual glyceryl trinitrate on the ABPI, claudication and maximum walking distance in patients with intermittent claudication

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Aim: To assess the immediate effect of sublingual glyceryl trinitrate (GTN) on the ankle brachial pressure index (ABPI), claudication distance (CD) and maximum walking distance (MWD) in patients with intermittent claudication.

Method: Inclusion criteria: I) history of intermittent claudication; II) resting ABPI of 1 or less; III) fall in ABPI of greater than 0·1 following exercise. Patients already on nitrates were excluded. Study 1. Following randomization to receive either 800 micrograms of sublingual GTN or placebo, patients (n=25) underwent a standardized exercise test. The post exercise ABPI was recorded. The crossover part of the study was then performed. Study 2. Patients (n=22) were exercised to their limit of tolerance at 3·2 km/h and their CD and MWD were measured. They were then randomized to either GTN or placebo spray and the exercise test repeated, recording the CD and MWD, followed by the crossover part of the study. Statistical analysis was by Wilcoxon Matched Pairs Signed Ranks Test.

Results:

		Placebo (median)	GTN (median)	*P*
Study 1	Post exercise ABPI	0·29	0·36	0·0001
Study 2	CD (IQ range)	70 m (50–80)	70 m (50–85)	0·5883
	MWD (IQ range)	105 m (80–172)	125 m (95–167)	0·0084

Conclusion: Sublingual GTN decreases the fall in ABPI following exercise and increases the maximum walking distance.

Can a measuring angiogram be used in place of a CT scan in the measurement of proximal neck dimensions in patients with ruptured AAA undergoing endovascular repair

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Aim: The management of patients presenting with ruptured abdominal aortic aneurysms (AAA) can be delayed in the process of gaining accurate proximal neck dimensions by computerized tomography (CT). Is it feasible to obtain these measurements by an on table measuring angiogram?

Methods: Fifteen patients undergoing elective endovascular repair of AAA had both preoperative spiral CT and on table measuring angiograms. The angiograms were reviewed blindly by two vascular registrars who measured proximal neck diameters and lengths. The mean of these measurements was compared to the CT dimensions. They then suggested the diameter of the proximal graft and whether or not a supra renal uncovered stent would be required. These results were compared to the actual size and configuration used.

Results: The mean maximum neck diameter as measured by the registrars was on nine occasions less than that on CT, on three occasions more than that on CT and on two occasions tied (P=0·09 Wilcoxon Matched Pairs). In eight patients the neck length was measured too short and in seven cases measured too long when compared to CT. This resulted in registrar 1 undersizing the graft in six cases, but equal or over sized in nine, and registrar 2 undersizing in four cases and equal or oversizing in 11. It also resulted in registrar 1 not using a supra renal stent in three cases as opposed to registrar 2 not using a supra renal stent in two cases in patients who did require these.

Conclusion: On table angiograms are poor at estimating neck length and emergency grafts should therefore have an uncovered supra renal stent. To oversize the proximal graft is better than to undersize. In 60–70 per cent of cases an appropriate graft size can be estimated from the on table angiogram alone.

Radiation exposure of the surgical team undertaking endovascular repair of abdominal aortic aneurysms

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Aims: The addition of endovascular techniques to the skills of a vascular surgeon may pose a risk of increased radiation exposure. We aim to quantify this risk and screening times with endovascular repair (EVR) of abdominal aortic aneurysms (AAA).

Method: Part 1. A retrospective study on the X-ray screening times of 140 cases of EVR of AAA. The type of graft used and the presence of a radiologist was recorded. The procedure was divided in those early and late in our experience of EVR of AAA. Part 2. A prospective study on six consecutive cases of EVR of AAA where theatre personnel were equipped with body radiation dose meters. In addition, the surgeon and assistant wore an ocular meter taped to the forehead. Radiation doses were measured conventionally.

Results: Part 1. The median screening time for EVR of AAA was 24·9 minutes (IQ range 17·2–33·8). There was no apparent learning curve when screening times between late and early cases were compared. There was however a significant increase in the median screening times for aorta uni-iliac grafts when compared to bifurcated grafts (24 vs 33 minutes, P=0·012). Presence of a radiologist did not influence screening times. Part 2. All body meters had total radiation dose less than the lowest measurable limit. The occular meters recorded 0·4 mSv and 0·3 mSv for the surgeon and assistant respectively.

Conclusion: EVR of AAA can be performed with minimal radiation dosage to the theatre personnel, although screening times for bifurcated grafts are longer than for aorta uni-iliac grafts.

Blood product requirements in patients undergoing elective endovascular repair of abdominal aortic aneurysms

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Aims: A prospective study was set up to investigate the effect of an endovascular programme on the blood transfusion requirements of patients undergoing elective aortic aneurysm surgery.

Methods: The blood product requirements of 132 patients undergoing elective endovascular repair using an aorta uni-iliac graft and femoro-femoral crossover (Group 1) was compared with the requirements of 35 patients undergoing conventional open repair (Group 2) and 37 patients undergoing femorofemoral crossover grafts alone (Group 3). Blood transfusion requirements were determined by intraoperative blood loss, clinical indication and postoperative haemoglobin concentration. Results are expressed as median (range).

Results:

	Blood loss (mls)	Number of units blood transfused
Group 1	500 (400–5500)	2 (0–38)
Group 1a (uncomplicated n=120)	500 (400–1500)	2 (0–12)
Group 1b (complicated n=12)	1550 (500–2900)	6 (0–38)
Group 2	1500 (400–5500)	3 (0–19)
Group 3	500 (200–1000)	0 (0–6)

Conclusion: Although measured blood loss is less in Group 1 this is not reflected in the use of blood products. Patients undergoing endovascular repair who require additional interventions were the highest consumers of blood products.

Assessment of patency rate and intimal hyperplasia in Heparin coated small vascular grafts

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Aims: Intimal hyperplasia (IH) represents a major cause of late failure in vascular grafts. Heparin shows a beneficial effect on long-term patency and prevents progression of intimal hyperplasia. Our aim was to assess patency rate and intimal hyperplasia formation in small calibre vascular grafts coated with Heparin.

Method: In 40 rats an infrarenal aortic interposition graft was implanted using sterile and microsurgical techniques. Two different types of graft were tested (Gore-tex and proprietary polyurethane [PU]) with and without Heparin coating. All animals survived 8 weeks after implantation. Area and volume of intimal hyperplasia and the per cent stenosis at the anastomoses and in the graft were measured.

Results: Untreated grafts showed a patency rate of 70 per cent for Gore-tex and 60 per cent for PU grafts. Heparin coated grafts showed 100 per cent patency in the Gore and 90 per cent patency in the PU group. All grafts showed intimal hyperplasia mainly at the anastomoses and it was significantly more pronounced in native PU than Gore-tex graft ($P<0\cdot05$). Heparin coating reduced significantly intimal hyperplasia at the anastomosis; namely 42 per cent for Gore-tex and 55 per cent for PU grafts.

Conclusions: Small grafts show an enhanced intimal hyperplasia at the graft anastomoses after eight weeks of implantation. Gore-tex grafts show significantly less intimal hyperplasia yielding a better patency rate. Heparin coating reduces significantly overall graft thrombosis but had no significant overall effect on intimal hyperplasia. Thus, Heparin coating seems to be beneficial for graft patency.

Patient benefit of cell washing during cardiac surgery

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Aims: Our aim was to influence the systemic inflammatory response syndrome (SIRS) during cardiac surgery by washing the autologous activated cardiopulmonary bypass (CPB) blood before retransfusion to the patient.

Methods: In a prospective randomized study CPB blood of 10 patients was processed by cell washing (CATS: Fresenius AG, Bad Homburg) or retransfused directly to 10 control patients without processing. Blood volume, processing time, haematology, blood chemistry, complement, coagulation and cytokine measurements were performed before and after CATS processing and before and after retransfusion to the patient on the ICU. Patient's outcome and adverse events were analysed.

Results: Mean values ± 1 SD of unprocessed (control) and washed (CATS) CPB blood.

Parameter	Control	CATS
fHb (mg/dl)	181·8±50·1	11·6±3·7
Heparin (IU/ml)	15·5±6·7	0·1±0·1
Prothrombin F1+F2 (nmol/l)	26·4±12·7	1·0±0·7
D-Dimers (mg/l)	28·5±15·4	1·7±1·5
C3a (ng/ml)	4731±2970	<269·5±32·6
C5b-9=TCC (ng/ml)	1993·7±479·1	<33·8±51·8
Il-6 (pg/ml)	1036·2±1245·2	30·7±22·4
Il-8 (pg/ml)	37·1±35·4	11·7±7·5

The washed autologous CATS concentrate yields a high transfusion effect (hematocrit 0·24 → 0·62) with a significant reduction of activated blood products (elimination rate >94 per cent; $P<0\cdot001$). In the control patients a transient significant elevation of the heparin concentration (0·1±0·5 – 1·5±0·7 IU/ml), plasma haemoglobin, complement (C3a/TCC) and cytokines (Il-6) was noted after retransfusion of unwashed blood. Three patients of the control and two patients of the CATS group showed postoperative adverse events which correlated to their intraoperative high mediator levels.

Conclusions: Blood washing with the CATS system yields a high quality autologous red cell concentrate. Due to the significant reduction of activated blood products a trend to reduce SIRS in the patient after cardiac surgery with cardiopulmonary bypass could be demonstrated.

Major lower limb amputation for vascular disease: outcome after rehabilitation

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Major lower limb amputation is often associated with poor outcome in terms of mobility. However, patients' initial mobility when measuring outcome is often not taken into account. The aim of the study was to investigate the final outcome when compared with preoperative mobility status. Eighty consecutive patients under the care of one surgeon who required major lower limb amputation for non-reconstructible occlusive arterial disease were studied. Prior to surgery mobility was assessed by the same physiotherapist (PW) using a modified Harold Wood Mobility Score. A detailed medical and surgical history was also taken. All patients were assessed for a prosthesis. Rehabilitation was maintained after no further benefit was deemed achievable. Mobility scores were again taken at the end of this period.

Sixty-one patients (77 per cent) were over the age of 65 and 26 patients (32 per cent) had diabetes. Twenty-five patients (31 per cent) had previous attempts at vascular reconstruction. Fifty-one per cent of patients had an above knee amputation while 46 per cent had a below knee amputation. Stump healing was a problem in 65 per cent of below knee amputations with a revision rate was 13 per cent. Twenty-nine per cent of patients died within three months of surgery. Prior to amputation 64 per cent of patients were housebound and 26 per cent were confined to a wheelchair due to pre-existing conditions. Postoperative scores show that 29 patients (57 per cent) of surviving patients were successfully rehabilitated to their preoperative status. Empirically derived mobility scores may not be an ideal measure of outcome and social, psychological and functional factors need to be taken into account.

Clinical behaviour and tumour risk factors for the prognosis of resectable ampullary carcinomas

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Aims: The purpose of this study was to analyse long-term prognosis after pancreaticoduodenectomy (PD) for ampullary carcinomas relative to clinical factors, nuclear composition and oncogenes.
Methods: Twenty-four consecutive patients with ampullary carcinomas who underwent PD between 1993 and 1996 participated in this study. Clinical variables included sex, age, duration of symptoms, alanine aminotransferase (s-ALT), aspartate aminotransferase (s-AST) and alkaline phosphatase. Morphological variables were tumour size, histological type, tumour differentiation, adenoma content and local lymph node invasion. Cell-cycle composition was evaluated with ploidy, percentage of phase 'S' cells and DNA index (DI). Proliferation markers included Cathepsine D in tumour and stroma, SPF tyrosin-kinase, Ki67 antigen, Topoisomerase II, erbB-2, EGFR, p53, CD31, bcl-2 and nm23. Multivariate survival analysis was obtained with Cox's regression proportional hazard model with these factors as covariates.
Results: Patient survival at 1 month, 1-, 2-, 3 yrs was 100, 92, 84 and 76 per cent. Cox's proportional hazard model revealed that a short duration of symptoms, tumour size, preoperative s-AST and DNA Index were independently correlated with a dismal prognosis:

Covariates	b coefficient	Significance	Hazard
Duration of symptoms (months)	−2·1881	0·0358	1·12
Tumour size (cm)	2·1937	0·0327	8·96
Preoperative s-AST (per 100 Units)	0·26	0·0768	1·3
DNA Index (DI)	3·2117	0·0436	24·82

Conclusions: Most of the tumour markers evaluated did not affect patient survival. However, DNA Index showed independently a strong risk increase. Since duration of symptoms and s-AST were associated with a low risk-increase, tumour size enhanced mortality risk eight times.

Endoscopic vs surgical biliary drainage for non-resectable ampullary carcinomas

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Aims: The objective of this study was to compare endoscopic vs surgical management respect short- and long-term outcome for non-resectable ampullary carcinomas.
Methods: We designed a prospective and randomized trial in which 52 consecutive patients since 1990 to 1997 with non-resectable ampullary carcinomas were treated. Non-resectability criteria included: age >75 yrs, morbid obesity, distant metastases and complete obstruction of the portal vein. Twenty-four patients underwent surgical drainage (hepatico-jejunostomy – 21, ampullectomy – 3). A definitive biliary endoprothesis was placed in the remaining 28 patients. Both groups were well-matched for sex, age, duration of symptoms, preoperative/pre-endoscopic serum bilirubin, alanine aminotransferase (s-ALT), aspartate aminotransferase (s-AST) and alkaline phosphatase. The mean follow-up was 14 months. Survival analysis was performed by Kaplan–Meier method and compared by log-rank test. Postoperative hospital stay and complication rate were compared by analysis of variance.
Results: Patient survival at 1-, 6-, and 12 months were 92, 84 and 48 per cent in the 'Surgery group', respectively; and 88, 76 and 34 per cent in the 'Endoscopic group'. There were no statistical differences respect overall survival (log-rank 0 3·47; P=0·062). Postoperative complication rate in the surgical group was 7/24 (29 per cent) and 7/28 (25 per cent) in the endoscopic group (P=0·24). Patients with endoprothesis showed a shorter hospital stay (6·2±1·1 vs 10·4±2·8 days; P<0·05).
Conclusions: Endoscopic biliary drainage is an adequate procedure in the management of non-resectable ampullary carcinomas, with similar survival and complication rate respect surgical treatment, and with a shorter hospital stay.

Congenital malformations of the gallbladder in the laparoscopic era

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Aim: The main objective is to determine the incidence of congenital malformations in surgery of the gallbladder because of the high risk of iatrogenic damage that may occur.
Methods: In a period of five years between November 1992 and November 1997, 470 laparoscopic cholecystectomies were performed, studying the described congenital malformations and the operative incidence of anatomical anomalies.
Results: There were congenital malformations in the 1·7 per cent of the cases: 1 agenesis of the gallbladder and cystic duct; 1 misplaced left lobe; 3 gallbladder hypoplasias (congenital vesicle diverticulo); 2 implants of the cystic in the right hepatic tract and 1 in the left. Moreover, 9 anomalies of the cystic artery (1·9 per cent) were diagnosed. All of them were intraoperative discoveries. Two patients were converted for anatomic verification. There were no intraoperative complications.
Conclusions:
1. One has to bear in mind the possibility of congenital malformations which has not been diagnosed previously.
2. In these cases the probability of injuring or cutting the extrahepatic biliary tracts is very high.
3. In case of anatomic incomprehension, conversion to open cholecystectomy is advised.

Bile peritonitis caused by congenital choledochal cyst perforation in an 8-month-old child: case report

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Aim: Bile peritonitis caused by congenital choledochal cyst perforation is a very rare surgical condition. This paper presents the experience acquired in diagnosis and surgical management of one infant.
Patient and methods: An 8-month-old male had been conservatively treated at the regional hospital for collapse, subsequent intermittent abdominal pain and vomiting for 5 days. On admission to our department he had fever and his abdomen was moderately distended with mild tenderness. Laboratory studies showed slightly elevated levels of total and conjugated bilirubin and SGOT. Abdominal ultrasound showed ascites. The diagnosis of generalized peritonitis was established and laparotomy was performed. Biliary peritonitis caused by congenital choledochal cyst perforation was found peroperatively. Because of established biliary peritonitis and the general clinical condition of the patient, external drainage was done via T-tube inserted through the perforation. Cholangiography 18 days after the operation confirmed type I choledochal cyst. A definitive operation, total cyst excision and Roux-en-Y hepaticojejunostomy (end-to-side) was performed one month after stabilization of the clinical status.
Results: There were no postoperative complications. Currently, he has been followed up for 20 months and is doing well.
Conclusions: Spontaneous perforation of a choledochal cyst is a very rare complication. Diagnosis is usually delayed due to nonspecific clinical manifestations and its exact establishment occurs mostly peroperatively. An external drainage of the bile via a T-tube is a preliminary procedure when urgent decompression is necessary. Subsequent total cyst excision and Roux-en-Y hepaticojejunostomy on an elective basis is the definitive surgical treatment.

The effect of vitamin E on plasma and liver free radicals in obstructive jaundice

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Objective: To observe the alterations of the free O_2 radicals in plasma and liver, and also the effects of vitamin E (α-tocopherol) – a strong antioxidant – to this alteration in obstructive jaundice.
Design: Experimental laboratory study.
Setting: Aegean University department of experimental surgery, Turkey.
Subjects: Twenty male Wistar rats.
Interventions: Through an upper midline incision a ligature was passed around the common bile duct in the sham-operated control group. In the group 2, the common bile duct was ligated with 4·0 silk and divided. Finally in group 3, the common bile duct was ligated and a subcutaneous dose of 20 mg/100 g body weight/day of vitamin E administered (Ephynal, Roche® – Turkey) from the 1st postoperative day for 15 days.
Main outcome measures: Plasma and liver malondialdehyde (MDA) – an available marker of free radicals and lipid peroxidation – were measured after 16 days of initial operation.
Results: Plasma and liver MDA values from group 2 [8·320 (1·360) nmol/ml–5·940 (0·776) nmol/ml] were significantly higher than the MDA values obtained from group 1 [2·573 (0·389) nmol/ml–3·544 (0·386) nmol/ml] ($P<0·005$, $P<0·005$). Although the plasma and liver MDA values of group 3 [4·680 (1·120) nmol/ml–5·219 (0·780) nmol/ml] were reduced remarkably when compared to group 2 [8·320 (1·360) nmol/ ml–5·940 (0·776) nmol/ml], it was not significant ($P>0·05$, $P>0·05$).
Conclusions: In this experimental study, significant elevation of MDA in plasma and liver suggest free radicals to be an effective factor in the pathogenesis of the hepatocyte injury in cholestasis. On the other hand, administration of vitamin E – one of the most effective antioxidant ever known – makes the increased plasma and liver lipid peroxide values to be reduced but this is not significant.

Intraoperative choledochoscopy as an alternative to intraoperative T-tube cholangiography in detecting retained stones in the biliary tree

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The aim of the study is to evaluate the success of the intraoperative choledochoscopy in detecting retained stones after classical cleaning of the bile ducts and to evaluate if its always necessary to perform intraoperative **T**-tube cholangiography to lower the incidence of retained calculi.

Since 1993, when we started with choledochoscopies till 1997, 153 choledochotomies were performed for choledocholithiasis. The patients were selected in three groups: in the first, only **T**-tube cholangiography was performed (87 cases), in the second only choledochoscopy (52 cases) and in the third group of 14 patients choledochoscopy was followed by **T**-tube cholangiography. Fifty per cent dilution of Telebrix were used for cholangiography. An Olympus T-20 fibercholedochoscope with 6 mm tip was used for the inspection of the biliary tree. In the first group, retained stones was found on postoperative **T**-tube biligraphy in 6 (6·9 per cent) patients, in the second group in 1 patient (1·9 per cent). In the third group no residual stone occurred. With choledochoscope we found in 46 per cent of cases more calculi after classical cleaning of the biliary tree. Choledochoscope was useful in the extraction or luxation of impacted calculi in the region of the papilla in 98 per cent, when these stones cannot be moved with other manipulation.

We conclude that in experienced hands intraoperative checking of the biliary tree with flexible choledochoscope is as effective as **T**-tube cholangiography. Lowering the duration of the operation and radiation exposure of the operating team is another advantage of this procedure.

Cellular and humoral immunity in the acute calculous cholecystitis

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Aim: The acute calculous cholecystitis is an acute inflammatory disease and to us seems a good model to study certain immunological parameters of response inflammatory of non-infectious origin.
Materials and methods: Following institutional ethics committee approval from Universitary Hospital of Valladolid and informed consent of patients, blood samples were obtained from 20 patients with acute calculous cholecystitis (Group 1). All blood samples were taken on the 1st day of diagnosis. A group of 20 volunteers served as controls (Group 2). The levels of TCD8, TCD4 and B lymphocytes, NK cells, immunoglobulins (Ig) G, M, A and IL-2 receptor (RIL-2) were measured in blood by flow cytometry, nephelometry and ELISA, respectively. The acute calculous cholecystitis diagnosis was performed by clinicals signs and symptons and the cholelithiasis by ultrasonography. Statistical analysis of data was performed using ANOVA-test and the Pearson-correlation test between groups, P-value <0·05 was considered significant.
Results: Groups were comparable in terms of anthropometric characteristics. Results are shown in the following table:

	Group 1	Group 2	Significance
TCD8 cells (%)	26·6±9·5	36·6±11·1	$P<0·05$
TCD4 cells (%)	39·8±11·1	40·9±10·2	NS
B lymphocytes (%)	13·9±6·4	8·1±3·4	$P<0·01$
IgG (UI/ml)	136·5±37·6	146±31·6	NS
IgM (UI/ml)	127·5±63·4	176±69·4	$P<0·05$
IgA (UI/ml)	202·6±89·8	169±51·4	NS
RIL-2 (pM)	141·2±81	57·6±28	$P<0·01$

Conclusions: RIL-2 which is the major growth factor for T-lymphocytes and the quantity of RIL-2 synthesized determines the size of the T-cell-dependent immune response. has an abrupt increase from the first day of acute-cholecystitis diagnosis.

Early repeat operations after gastric resection for peptic ulcer disease

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Presented are a 12-year follow-up of patients with repeat operations after gastric resection by Bilroth I and Bilroth II for peptic ulcer disease. The reasons for the repeat operations were: (1) diffuse peritonitis (duodenal vault insufficiency or anastomosic leak); (2) intra-abdominal abscess (subphrenical, subhepatic); (3) eventeration; (4) intra-abdominal haemorrhage or haemorrhage in the gastric lumen (poor haemostasis, stress ulcers, haemorrhagic gastritis, ulcer remnants etc.); (5) early ileus; (6) lack of patency in the anastomosis – stenosis, anastomositis, outside pressure etc.; (7) acute postoperative pancreatitis; (8) complications from the biliary tree; (9) others.

The following surgical interventions were carried out: re-laparotomy, haemostasis, lavage, resection, debridment, gastro-intestinal anastomosis. Good results were observed. Only nine patients died.

We can reach the following conclusions from the results:

1. Re-laparotomies were 4·7 per cent from our cases.
2. The most frequent indication for re-laparotomy was postoperative pancreatitis, haemorrhage end diffuse peritonitis.
3. Mortality among the re-operated patients was 33·3 per cent.
4. Laparostomy and programmed lavage is recommended as a way of reducing mortality.

Operative internal drainage of bile ducts

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Reconstructing operations, performed on extrahepatic bile ducts, usually need protection of anastomosis by means of drainage. Classic Kehr's drainage is loaded by risk of complications. Since 1993 the authors have been applying the alternative way of drainage: an intraduodenal drainage by endoprothesis Y (DEY). Endoscopical removing of the drain was performed in 3–4 months after the operation. This way of drainage was used between March 1993–May 1997 in 23 patients. We did not observe any complications or pancreatic reactions. Clinical control of patients was made after operation with ECW. In four cases the late results of treatment were unsuccessful. In the other 16 patients the results of performed operations were favourable.

Conclusion: Proposed way of protection of bile ducts reconstructions using (DEY) we noticed fewer complications in comparison with analogus group of patients protected by classic Kehr's drainage.

Keywords: Iatrogenic diseases, drainage bile ducts, common bile ducts (CBD).

Acute dilatation of the choledochal cyst masquerading as an acute abdomen

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Introduction: The choledochal cyst is the predominant feature of a constellation of anomalies involving the pancreatobiliary system. The classic symptom complex of pain, mass, and jaundice is in fact encountered infrequently. This is a case of a 26-year-old pregnant woman presenting with acute dilatation of choledochal cyst masking acute abdomen.

Case report: The patient was admitted to emergency department with symptoms of severe abdominal pain, nausea and vomiting of 2 days' duration. In laboratory studies, liver enzymes, direct and indirect bilirubin levels were found to be high, while amylase and lipase levels were normal. She had abdominal guarding and rebound tenderness on all quadrants in physical examination. Abdominal ultrasonography revealed a distended gallbladder with thicken wall but without gallstones, and a cystic lesion, 5 cm in diameter, located behind the head of the pancreas. The patient underwent emergency laparotomy with a preoperative diagnosis of acute acalculous cholecystitis. During laparotomy type I choledochal cyst and annular pancreas was found. Since the patient was pregnant and no real cause of acute abdomen was found, the abdomen was closed without performing any procedure for further investigation. Further ultrasonographic examinations revealed a rapid increase in the diameter of the cyst, reaching 12 cm in 5 days and detected debris at the bottom of the cyst. Obstruction of the cystic outlet and acute dilatation of the cyst was suggested to be the cause of severe symptoms and signs. Since the patient had ongoing severe abdominal pain, percutaneous drainage of the cyst was thought to be appropriate for symptomatic relief. Pain relief was obtained immediately after the drainage of the cyst. Meanwhile preterm labour occurred. Cystography performed by means of a pig-tail catheter after the preterm labour showed the complete obstruction of the cystic outlet. After a week of drainage, ERCP was performed but the possible relation of the cyst with pancreatic duct could not be shown, probably because of the persistent obstruction. ERCP was repeated in 10 days and showed the choledochal cyst opening directly into the main pancreatic duct. The patient underwent laparotomy for definitive treatment. Since the cyst had intrapancreatic extension, pylorus preserving pancreaticoduodenectomy was performed to resect all of the lesion.

Conclusion: Choledochal cysts usually fail to contract, resulting in poor emptying and significant stasis of bile and debris. Obstruction of the cystic outlet by thick bile and debris may lead acute dilatation of the cyst masquerading as an acute abdomen.

Treatment of calculous acute cholangitis: results of a surgical management

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Aim: This retrospective study presents the results of a complete surgical management in the treatment of calculous acute cholangitis (CAC). Its principle is to obtain rapid and complete clearance of the common bile duct (CBD) from stones avoiding thus, endoscopic sphincterotomy (ES) as primary treatment of CAC. This latter is not always easy to perform, is not available everywhere and results in about one to two per cent in acute pancreatitis. Surgical treatment is proposed as a valuable alternative to ES.

Material and methods: Fifty-four patients with a mean age of 76 years having CAC, have been operated on from 1983 to 1993. Thirty-eight (70·4 per cent) patients have been operated on as an emergency and 16 (29·6 per cent) patients between 2 and 6 days after admission. Operation consisted in obtaining rapid and complete clearance of the common bile duct (CBD) from stones, which was controlled intraoperatively by flexible choledochoscopy. CBD was then immediately closed without biliary drainage in 50 (92·5 per cent) patients. During the same period, no ES was performed as first treatment of cholangitis but one patient required this latter postoperatively.

Results: There were no postoperative deaths. Fifty-two patients (96·2 per cent) had no biliary complications and 13 (24 per cent) patients had general complications especially respiratory and cardiovascular complications. Patients were discharged from hospital 13·6 (±6·9) days after operation.

Conclusion: Despite opposite opinions, we do not advocate the use of primary ES in the treatment of CAC. The benefits of this technique is to confirm normal biliary tract anatomy, to remove the gallbladder which was found to be infected in more than 40 per cent of the patients, and to avoid ES's complications. Considering this series results, the place of surgery should be reconsidered and compared to endoscopic sphincterotomy by further comparative studies. Still, it represents a secure alternative to ES especially if ES is not easily available nor easy to perform.

Results of gallbladder carcinoma treatment using radical surgery

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Primary gallbladder carcinoma (GBCA) is generally a rare disease, but the most frequent neoplasm of extrahepatic biliary ducts and constitutes about one per cent of reasons for biliary duct surgery. Prognosis in patients coming to surgery with clinically apparent cancer is very poor. Gallbladder carcinoma spreads to the liver by direct invasion and by lymphatic vessels to periportal and pancreatico-duodenal lymph nodes. In the years 1972–1997 74 patients were treated for GBCA. Most of those patients (53) had no preoperative diagnosis of GBCA. Up to 1991 the only operation performed was cholecystectomy. Since 1991 21 patients were operated on for GBCA, in whom preoperative diagnosis was stated on a basis of clinical symptoms, USG and CT examinations and confirmed intraoperatively by histological examination. Eleven of carcinomas were found by incidental intraoperative histological examination. In 16 patients cholecystectomy and extend lymph node dissection were performed. In 7 patients only transhepatic bile duct drainage was applied. In 9 cholecystectomy and hepatic resection-segment IV and V, with extend lymph node resection were performed. Postoperative period was complicated by small bile leakage in one case with simultaneous resection of hepatic ducts bifurcation. Follow up observation period ranges from 1 to 6 years. We observed 2 to 6 months' survival in 49 patients operated on for advanced GBCA and 18 to 20 months' survival in 24 patients who underwent extend lymph node dissection or hepatic segmentectomy and extend lymph node dissection. One patient stays in our observation in very good health 6 years after segmentectomy and lymph node dissection. In our experience we can conclude that radical operation for gbca seems to be justifiable because survival of those patients is remarkably longer which is in accordance with data given by other authors.

The latest case of Mr Sherlock Holmes: the modern Dr Watsons use HCTCA!

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Aim: To detect the cause of dilation of right hepatic bile ducts and a postoperative biloma after a laparoscopic cholecystectomy
Materials and methods: Laparoscopic cholecystectomy, US, US guided drainage, laboratory investigations, Helical CT Cholangiography (HCTCA)
Case report: A 33-year-old woman was treated with laparoscopic cholecystectomy in another hospital. Because she did not feel well postoperatively, she was investigated by ultrasound
Medical certificate A cystic mass in the gallblader bed and dilation of the bile ducts in the right hepatic lobe.

An ultrasound guided cystic drainage was performed and it proved the presence of a biloma Helical CT Cholangiography was recommended
The result of the investigation by HCTCA Postoperative situation Gallbladder is removed. The postoperative state is also illustrated by metallic clips. The enhancement of bile is good Bile ducts are shown well The diameter of common bile duct is normal There is some contrast material in the duodenal lumen There is considerable dilation of bile ducts in the right hepatic lobe The bile ducts in the left lobe are normal

Dr Watson performed a MIP and an SSD and gave the opinion that the right hepatic duct of atypical course had been ligated while clipping the cystic duct This led to the formation of a fistula and a subsequent biloma The passage of bile from the left lobe was unhindered, therefore jaundice was not observed
Conclusions: The surgical situation corroborated the finding of HCTCA

The so-called 'post-cholecystectomy syndrome' – a myth or reality?

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After removal of the gallbladder 10–30 per cent of patients present with persisting various symptoms which are often called by the name of 'post-cholecystectomy syndrome'. In order to establish the cause of the complaints – 83 such patients were subjected to thorough clinical investigations, enzymatic liver and pancreas function tests, abdominal ultrasound, isotope scanning, ERCP and CT.

In 24 cases (30 per cent) the complaints related to the hepatobiliary system They were caused among other things by cholangitis or stenosis of the papilla Vateri

More frequently (in 55 cases – 67 per cent) they were due to other diseased organs, predominantly the stomach, duodenum, pancreas and large intestine The studies have shown that in 47 per cent of patients the symptoms were caused by a clearly defined disease entity
Conclusions:
1 In patients with symptoms persisting after cholecystectomy in 63 per cent can find the cause of their complaints, in 67 per cent of cases the cause was unrelated to the hepato-biliary system
2 The term 'post cholecystectomy syndrome' should not be used because it exempts ostensibly the physician from undertaking further diagnostic investigations into actual causes of patient's complaints

How can helical CT cholangiography (HCTCA) help surgeons in hunting for hidden bile duct stones?

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Aim: The high resolution capability of the spiral CT gave us a tool for the imaging of hidden bile duct stones and the other abnormalities of the bile ducts. Our aim was to point out the role and the place of HCTCA in the diagnostic algorithm
Materials and methods: Forty-eight patients were investigated by a spiral CT scanner. A hepatotrop contrast material was adjusted intravenously in order to reach reasonable opacification in the biliary system According to the optimal filling rates the pictures were taken delayed in two series. The pictures were evaluated in a common view and by MPR and 3D rendering MIP and SSD postprocessing methods
Results: With this method calculi were seen the common bile duct, the cystic duct, the main hepatic ducts and its secondary – and sometimes even smaller intrahepatic branches of those The bile passage toward the duodenum could be imaged in all cases.

Biliary stones were demonstrated in six cases None of them caused completed passage disturbance of the bile In two cases we could show miniature residual calculi in the little intrahepatic branches
Conclusions: In the diagnostic algorithm ultrasound has the essential role in the imaging of biliary pathologies Endoscopy seems to be tending more therapeutic than only diagnostic intervention.

According our experience the HCTCT has a main role in the differential diagnosis of bile duct dilatation We could clearly establish whether in the background of the passage disturbance was an intraductal or periductal lesion or a sclerosis of the Vater papilla

All of our cases were proved by EST or by operation

Gallbladder motility after gastric surgery estimated by infusion cholescintigraphy

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The aim of the study is the estimation of the gallbladder (GB) motility in the controls (C, n=8), patients after partial gastrectomy (Billroth I – B I, n=7 and Billorth II – B II, n=7), gastroplasty (G, n=7) and in those after total gastrectomy (PG, n=10) in order to assess the influence of the truncal vagotomy (GP, PG) and exclusion of the duodenal transit (B II, PG) of food on the GB motility

The study was performed during (3 h, 10 ml/h) infusion of 150 MBq, 0·25 mg/ml 99m-Tc-EHIDA, preceded by a loading dose. Test meal was given in 120 min

In the patients with preserved n vagus and duodenal transit (BI), ejection fraction (EF=66·4±9·2 per cent), emptying time (ET=35·1±6·2 min) and ejection rate (ER=2·1±0·5 per cent/min) were almost physiological ($P>0{\cdot}05$) (C, EF=76·7±17·9 per cent; ET=37·8±11·4 min and ER=2·1±0·45 per cent/min). In the patients with exclusion of duodenal transit (RV BII), EF values were (58·3±11·4 per cent) slightly, but not significantly decreased ($P<0{\cdot}05$) in comparison to C and RV BI while ET and ER were completely undisturbed (39·0 min and 1·61±0·46 per cent/min) In those with truncal vagotomy (GP), EF was slightly decreased (54·4±14·4 per cent), ER unchanged (1·8±0·84 per cent/min) while ET (23·3±7·5 min) was significantly ($P<0{\cdot}05$) decreased in comparison to C, RV BI and RV BII. In the PG, with both truncal vagotomy and exclusion of the duodenal transit, EF, ET and ER (23·3±8·5 per cent, 23·5±7·6 min, 0·92±0·40 per cent/min) were significantly ($P<0{\cdot}05$) decreased in comparison to C, RV BI, RV BII andGP

We can conclude that truncal vagotomy, especially if accompanied by the exclusion of duodenal transit cause GB motility disorders So, in the choice of gastric surgery, advantage must be given to the methods that preserve n vagus and duodenal transit as often as it can, in order to avoid formation of GB calculosis

Combined ERCP and laparoscopic cholecystectomy in the management of choledocholithiasis

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The authors present a series of 70 cases of choledocholithiasis managed by removal of the common duct stones by endoscopic sphinterotomy followed by laparoscopic cholecystectomy They represent the 12 per cent of the total 600 laparoscopic cholecystectomies performed between March 1992 and December 1997. Ten cases out of 70 had to be converted to open operation.

Indications of ERCP+VLC:

(70 cases)	– Cholestasis without jaundice	30
	– Acute pancreatitis with choledocholithiasis without jaundice	18
	– Acute pancreatitis with choledocholithiasis with jaundice	4
	– Choledocholithiasis with jaundice	16
	– Ampullary stenosis	2
Converted VLC (10/70)		
	– Adhesions	7
	– Haemorrhagic complication	2
	– Duodenal perforation	1

Conclusions: The complete mini-invasive management of choledocholithiasis appears preferable to the standard open techniques.

Microlaparotomy in the management of cystic duct stump syndrome

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Cholecystectomy is an established successful operation which provides total relief of presurgical symptoms in up to 85 per cent of patients. About 5 per cent of patients after cholecystectomy experience severe episodes of upper abdominal pain. These so called postcholecystectomy syndromes may be due to biliary strictures, retained biliary calculi, cystic duct stump syndrome, stenosis or dyskinesis of the sphincter of Oddi. Postcholecystectomy symptoms caused by cystic stump and gallbladder remnant had been described early this century. During recent years laparoscopic cholecystectomy became popular but we have not found in the literature the mention of either that it could cause cystic duct stump syndrome or it could be used for its treatment. During the last 8 years in 10 patients we found gallbladder remnants or cystic duct stumps causing their symptoms. Among the 10 patients 3 had laparoscopic and 7 classic cholecystectomy. After incomplete cholecystectomy we usually find that the cystic duct stump and the Calot triangle embedded in inflamed scar tissue. For this reason the surgical risk is too high with laparoscopic surgery to reoperate for these pathological changes. In all 10 cases the pathological cystic duct stump and gallbladder remnants were removed using 3–4 cm single microlaparotomy incisions. The postoperative stay of these patients were uneventful and they were discharged home 2–3 days after surgery.

Microlaparotomy cholecystectomy in the treatment of Mirizzi's syndrome

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An impacted gallstone in the cystic duct with subsequent inflammation and edema resulting in extrinsic compression of common bile or hepatic duct with jaundice is known as Mirizzi's syndrome. The Mirizzi's syndrome presents a difficult surgical challenge because the dense adhesions and edematous inflammatory tissue cause distortion of the normal anatomy in Calot's triangle, leading to a great risk of bile duct injury. Therefore, a controversial issue the surgical strategy for the treatment of Mirizzi's syndrome since the introduction of laparoscopic cholecystectomy. The present study was undertaken to elucidate the applicability of microlaparotomy cholecystectomy (MLC) in the management of Mirizzi's syndrome. Between December 1990 and December 1997 we operated on 18 patients for Mirizzi's syndrome with micro and minilaparotomy. In 16 of these patients had type I of Mirizzi's syndrome, the remaining 2 had type II of this syndrome. In 15 of these patients the gallbladder was removed using 3–4 cm single microlaparotomy incisions. In the remaining 3 patients using 5·5 cm, 8 cm as well as 12 cm long incisions for the removal of the gallbladder, and placement a distal T tube because of stenosis of the common hepatic duct, suture repair of the choledochal defect as well as choledochoplasty. In the early stages, presented within seven days of the acute edema does not make MLC more difficult. In 14 of these patients the MLC were done within seven days of the onset of the obstructive cholecystitis. The postoperative stay of these patients were uneventful and they were discharged home 3 days after surgery.

Surgery of the benign biliary strictures

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Although there have been great developments at diagnosis and treatment of biliary system surgery, benign biliary strictures are still important clinical problem. Twelve patients with biliary strictures were studied retrospectively for their diagnosis and treatment. All patients previously underwent biliary surgery and had high blood alkaline phosphatase levels. PTC and ERCP were gold standards for diagnosis of stricture site. Ten patients were diagnosed with the low level (Bismuth Grade I–II) and two of them high level (Bismuth Grade III–IV) strictures. Three of twelve patients were transferred after the laparoscopic bile duct injury. Eight patients had excellent surgical outcome in a 15-month follow-up period. Roux-en-Y hepaticojejunostomy and/or choledochojejunostomy are the best surgical procedures for treatment of benign bile duct injuries in our experience.

Preoperative ultrasound to predict technical difficulties of conventional cholecystectomy

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Ultrasonography is a safe, cheap, easy and most frequently used non-invasive radiological examination for the diagnosis of gallbladder disease. This study was designed to investigate the success of preoperative ultrasonography to predict technical difficulties of conventional open cholecystectomy.

Twenty-seven patients participated in this study on whom were performed open cholecystectomy operations. Patients who were hospitalized with the diagnosis of cholelithiasis were examinaed by ultrasound again the day before cholecystectomy. The morphology, view (distented, contracted), size, volume and wall thickness of gallbladder, number and sizes of calculi and presence of cholesterolosis, polyps in gallbladder, diameter of common bile duct, presence of pericholecystic fluid collection, appearance of the intrahepatic ducts, päncreas and liver were investigated. After the conventional cholecystectomy operations, the degree of difficulties was determined postoperatively using visual analogue scale (VAS, 0–10). The scoring was used for intraperitoneal and gallbladder adhesions, dissections of cystic artery, cystic duct and gallbladder bed. Bleeding duration of operation, using of drain and presence of complication were noted.

Gallbladder volume, number of calculi and presence of cholesterolosis were significantly associated with operative difficulties (Student's t, $P<0{\cdot}05$). The other parameters are not seen as a predictor of operative difficulties. Although preoperative ultrasound can be useful, it is not enough to predict technical difficulties of conventional cholecystectomy.

Malignant biliary tract jaundice

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Aim: After lithiasis, tumours are the most common surgically managed processes of the biliary tract. In this sense, gallbladder carcinoma predominates (80 per cent), followed by tumours of the biliary tree (10 per cent) and Vater's ampulla (10 per cent). Malignant jaundice is the most common presentation of such processes. We report our experience with this entity over a 6-year period.

Materials and methods: A total of 79 patients suffered malignant jaundice in the period between January 1991 and December 1996. The three most frequent underlying tumours were gallbladder lesions, extra- and intrahepatic biliary tree neoplasms and tumours affecting Vater's ampulla. The incidence, diagnostic methods, treatment protocols and morbidity and mortality are evaluated.
Results: There were 47 females and 32 males (mean age 72·8 years, range 36–86). Routine investigations (ultrasound, computed tomography, endoscopic retrograde cholangio-pancreatography and transparietohepatic puncture) established the diagnosis in 69 per cent of cases. The diagnosis was established at laparotomy in 26 per cent of cases, and by histopathological study in 5 per cent. Extrahepatic biliary tract cholangiocarcinoma was the most common lesion (48·1 per cent), followed by gallbladder tumours (29·1 per cent) and neoplasms of Vater's ampulla (18·9 per cent); cholangio-carcinomas were the least frequent (3·9 per cent). A total of 44 patients were operated upon (55·6 per cent). There were 12 exploratory laparotomies. A total of 17 biliary stents were placed, and 8 external biliary bypasses were made via transparietohepatic puncture – 5 being definitive. There was no treatment in 14 cases (17·7 per cent). Immediate mortality was 34·1 per cent (n=27). There were no cholangitis episodes after placing autoexpanding stents.
Conclusion: Biliary tract tumours have a poor prognosis due to late diagnosis, rapid progression and near-lying tissue infiltration. Surgery does not tend to be curative; hence alternative, effective and scantly aggressive palliative measures should be evaluated.

Clinical, laboratory, operative differences in patients with malignant and benign biliary tract obstructions

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Aim: Biliary tract obstruction is an important and common clinical condition which usually demands surgical relief. The cause of obstruction determines outcome of patients. We conducted this study to clarify whether malignant and benign biliary tract obstructions have different effects on clinical, laboratory and operative factors.
Patients and methods: Thirty-six clinical, laboratory and operative parameters were analysed in 107 patients. There were 52 females and 55 males, with a mean age of 60 (ranged 24–87) years. The cause of obstruction was common bile duct stone (n=65) and malignancy (n=62). All patients in this study had surgical relief of jaundice. Those patients who did not undergo surgical biliary drainage were not included in this study (stone extraction by ERCP in 14 patients, laparotomy and/or biopsy in 7 patients with malignancy). The factors evaluated in these patients were: age, sex, weight loss, diabetus mellitus, previous surgery, history of smoking, concomitant medical disease, fever, Murphy's sign, clinical evidence of cholangitis, preoperative hospitalization time, preoperative ERCP, positive cultures, pre- and postoperative blood transfusions, preoperative oral intake, pre and postoperative total parenteral nutrition, operation time, postoperative complications, postoperative mortality, postoperative antibiotic usage, postoperative drainage time, pre and postoperative nasogastric tube drainage time, haematocrit, haemoglobulin, white blood count, platelet, blood urea nitrogen, creatinine, albumin, bilirubin, serum glutamic oxaloacetic (SGOT) and pyruvate (SGPT) transaminases and alkaline phosphatase. The chi-square test was used for statistical analysis.
Results: Those patients with malignant obstruction were found to have significantly high rates of weight loss, history of smoking, preoperative ERCP, high levels of SGOT, SGPT and bilirubin; pre- and postoperative blood transfusions, pre and postoperative total parenteral nutrition, postoperative complications and mortality statistically. Additionally those patients had longer operation, pre- and postoperative nasogastric tube drainage and postoperative drainage time. The rates of high creatinine levels and presence of Murphy's sign were found to be high in patients with benign obstruction.
Conclusion: Patients with malign biliary tract obstruction have high rates of postoperative morbidity and mortality compared with patients with benign obstruction. This may be due to severe disturbance of hepatocellular functions in these patients. Renal functions should be monitored carefully in patients with benign biliary tract obstruction.

Liver

Hepatic hydatid disease and therapeutic approach

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Hepatic hydatid disease is one of the most important public health problems in our country. There are many different types of surgical approaches for hydatid disease of liver. We investigated 112 cases with hepatic hydatid disease treated surgically in our clinic for the last 10 years. Eighty-one patients were female (72·3 per cent) and 31 patients were male (27·7 per cent). Seventy-seven per cent of cases were admitted with the complaint of abdominal pain, 13 per cent with abdominal distention, 7 per cent with jaundice, 4·3 per cent with abdominal mass.

Eighteen patients (16·07 per cent) had recurrence. The most commonly used radiological method to demonstrate the lesion was ultrasonography (80 per cent). In 67·85 per cent of cases right lobe was involved and the lesion side was left lobe in 26·78 per cent of cases and 5·35 per cent of cases was bilateral.

In 112 patients 145 totally different cysts were found. Cysts were infected in 23 patients (20·50 per cent) and incorporated bile duct branches in 24 patients (21·42 per cent). The surgical approach was as shown below:

We preferred intraflection for 35 patients, omentoplasty for 33 patients, cystotomy + drainage for 26 patients, capitonage for 18 patients, total cystectomy for 13 patients, hepatectomy for 2 patients and aspiration for 1 case.

Most common complication was bile fistula. It was seen 14 per cent of patients. The discharging period varied between 9 and 147 days. Generally, complications occurred after cystotomy and drainage procedures. The most common preferred technique was intraflection. Different methods were used according to location of the lesion and condition of the patient. Of the available options, drainage was useful depending on the location of the cysts and in infected cases.

Comparison of different surgical methods performed for hepatic hydatid disease of the liver

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Aim: Hydatid disease of the liver is highly prevalent in Mediterranean countries, in which the population live mostly in rural areas. Although the taking out of the cyst itself is rather easy, management of cystic cavity is usually very difficult. The outcome of surgical methods used in management of cystic cavity with or without drainage in patients with hepatic hydatid disease was evaluated.

Materials and methods: Three hundred and forty consecutive patients who admitted to Department of General Surgery between 1988 and 1996 with hepatic hydatid disease were reviewed retrospectively. In the first group surgical methods without drainage such as cystectomy (n=11), capitonnage (n=55), omentoplasty (n=91) and capitonnage + omentoplasty (n=53), in the second group surgery with drainage such as external drainage (n=74), internal drainage (n=7), and combined methods (n=21) were applied. Role of symptoms and physical findings, types of surgical management, complication rate, hospitalization period, mortality and recurrence rates were evaluated.

Results: Complication rate, average hospitalization period, recurrence and mortality rates were 12·5 per cent, 9·5 days, 9·9 per cent and 0 per cent respectively in patients without drainage and 63·7 per cent, 26·5 days, 12·7 per cent and 0·9 per cent respectively in patients with drainage. The complication rate and hospitalization period in the group with drainage was significantly higher (P<0·001) than those of the group without drainage.

Conclusions: It is concluded that surgical treatment of hydatid disease of the liver without drainage decreases postoperative complication rate and average hospitalization period. Either drainage or non-drainage of cystic cavity has no effect on recurrence.

Pyogenic liver abscess in the elderly

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Aim: To present our experience in pyogenic liver abscess (PLA) in the elderly to try to analyse the clinical, diagnostic and therapeutic behaviour in this type of patient.

Materials and methods: From January 1985 to December 1995, 67 patients with PLA were treated in our units. These patients have been divided into two groups: under 61 years (32 cases) and over 60 years (35 cases). The mean age was 41·2±12·6 years and 73±6·7 years, respectively. Clinical features, associated diseases, laboratory test, imaging and microbiological findings, modality of treatment, associated surgery, morbidity and mortality were retrospectively assessed and compared in both groups. Statistical analysis was done by the χ^2 test for qualitative data and Student's t-test for quantitative data. Significance was taken at P<0·05.

Results: The pathogenesis of PLA by direct extension from an inflammatory process in adjacent structures was found most frequently in the elderly [7/32 (21·8 per cent) vs 17/35 (48·5 per cent), P=0·02]. In the same way, multiple abscesses appeared mainly in the elderly [5/32 (15·6 per cent) vs 13/35 (37·1 per cent), P=0·04]. Between the two groups there were no significant statistical difference referred to sex, symptoms and signs, APACHE II score, associated diseases, laboratory findings, size and location of the lesion, microbiologic data, method of treatment (antibiotics alone, percutaneous drainage, surgical drainage), associated surgery, morbidity and mortality.

Conclusions:

1. The pathogenic factor mainly in the elderly was an infection by direct spread.
2. There was no significant difference in the clinical and biological behaviour in the elderly with respect to younger patients.
3. Multiple abscesses were more frequently found in the elderly.
4. Neither in morbidity nor in mortality were there significant differences between the two groups of patients so age is not a risk factor in patients with this condition.

Hydatic disease of the liver: report of 304 cases

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Aim: To investigate the management of the patients with hepatic hydatic disease retrospectively.

Patients and methods: Three hundred and four patients with hepatic hydatosis were operated between 1981 and 1996.

Results: Cysts were found in the right lobe in 238 patients, in the left lobe in 41 patients and bilateral in 25 patients. Forty-five patients had multiple hepatic and 18 had co-existing cysts in spleen, pancreas, adrenal gland, mesocolon, over, retroperitoneum, and abdominal wall. The diameters of the cysts were smaller than 5 cm in 13·5–10 cm in 106 and larger than 10 cm in 185 patients. There were infected cysts in 35 patients. The most frequent symptoms were upper abdominal pain and tenderness, fever, and less frequent jaundice and pruritis. Three patients were admitted with acute abdomen due to cyst perforation. Surgical procedures were partial cystectomy and drainage in 122, capitonage in 95, omentoplasty in 40, cyst excision in 22, segmentectomy in 10, and cystoenterostomy in 10 patients. Co-existent cysts were treated by splenectomy, oophorectomy and cyst excision. Ten patients with partial cystectomy and drainage developed chronic biliary fistula. No recurrence was seen in follow-up lasting from 3 months to 6 years. Povidone iodine, 20 per cent hypertonic saline solution and 95 per cent ethanol were used as scolosidal agents. Four patients died of unrelated causes.

Conclusion: Management of hydatic disease of the liver with capitonage, omentoplasty, cyst excision, segmentectomy, and cystoenterostomy are superior to tube drainage.

Liver resections for primary hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide with a poor prognosis and a high recurrence rate. Aim of this study was to review our results in 14 patients resected for HCC in the last 5 years.

Methods: From 1992 to 1997 14 patients underwent partial liver resection for primary HCC. There were 8 male and 6 female patients with a mean age of 68 years (range 30 to 73 years). Underlying cirrhosis was present in 9 of 14 patients. Tumour staging was assessed by ultrasonography. CT-scan and preoperative angiography. Three patients were stage I; five were II; 4 were III and 2 were IVa. HCC was single in 10 patients and multiple in 4 and the mean size was 5·8±4·2 cm. Types of resection were: right hepatectomy in 3 patients, left hepatectomy in 5, bisegmentectomy in 2, 1 segmentectomy, 2 subsegmentectomies and 1 atypical resection. Nine patients were pre-operatively treated by chemo-embolization (TAE). Synchronous metastasis was observed in 4 patients at time of surgery, and surgery was not curative in 2. Median follow-up was 24 months.

Results: Post-operative complications occurred in 3 patients: 2 cases of liver failure (14 per cent) and 1 pneumonia (7 per cent) with a total morbidity rate of 21 per cent. Recurrence in the liver was noticed in 4 patients with underlying liver cirrhosis (28 per cent). Mean time between surgery and HCC recurrence was 166 days (range 58 to 275 days). No peri-operative mortality was seen and overall mortality rate is 14 per cent. Two patients died within the first year because of local tumour recurrence. Overall patient survival and disease-free survival is 81 per cent and 74 per cent at 1 year respectively.

Conclusions: Despite a total low morbidity rate, HCC recurrence is still high especially in cirrhotic patients with a considerable risk of postoperative liver failure. The incidence of distant metastasis is rather low in our experience. We think that liver resection can be proposed as therapy of choice in selected patients with good liver function and localized HCC. Adequate pre-operative evaluation is mandatory to improve results.

Two stage hepatectomy in metastatic tumour invading right and middle hepatic veins

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Aim: Authors present the case of two stage operation in metastatic tumour from renal cell carcinoma located in segments 4 and 8 of the liver.

Case: Thirty-eight year old female patient was admitted to our department with 8 cm liver tumour 5 years after left nephrectomy. CT scans and power Doppler ultrasound have shown possible invasion of right and middle hepatic veins. With total liver volume of 1902 cm^3, the volume of segments 2 and 3 was insufficient to perform extended right hepatectomy with adequate tumour free margin.

Instead, right portal vein ligation and hepatoduodenal ligament lymphadenectomy was performed. She underwent this procedure on 7th February 1997. There was as extrahepatic malignancy. Postoperative course was complicated with massive right pleural effusion. In successive spiral CT scans performed 4 and 8 weeks after portal vein ligation total liver volume did not change significantly (1933 cm^3) but the volume of planned remnant liver segments 2 and 3 was estimated as insufficient.

We estimated this volume as satisfied and safe in 11 postoperative week. On 29th April the patient underwent right extended hepatectomy without any complications in postoperative period. Total volume of resected liver was 1120 cm^3 with approximately 750 cm^3 of remmant tissue. Twelve weeks after secondary operation segment 1+2+3 volume reached 1200 cm^3 and is stable up to last CT control performed on 19th December 1997. The patient has shown no signs of liver insufficiency or recurrence after both procedures.

Conclusion: In the well differentiating neoplasms there is time to wait long enough until the regeneration of unligated lobe will be satisfactory prior to hepatic resection.

Therapeutic strategy in the treatment of liver abscess: our experience

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The last 10 years we have treated 44 patients with liver abscess. Initially we have examined the general symptomatic conditions (APACHE), the ultrasonography lesion characteristics, and the presumed aetiology.

The first therapeutic approach consisted in specific antibiotic therapy associated with execution of percutaneous ultrasound-guided drainage. We have valued, successively, aetiology, drainage capacity and change of clinical symptoms examining biochemical and clinic parameters (fever, septic condition).

These parameters valued every 12 hours have been correlated with percutaneous drainage success. Only five patients needed another therapeutic approach (chemotherapy with intraportal catheter) or surgery by laparotomy. There were no deaths.

Correction of hypersplenism on liver cirrhosis patients

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Syndrome of the secondary hypersplenism is the serious complication of the portal hypertension on liver cirrhosis. One hundred and twenty-five patients with liver cirrhosis were studied. The moderate cytopenia in the peripheral blood was marked in 41 and significant – in 84 patients. Gastroesophageal varices were noted in 108 patients. 53 patients had a bleeding in anamnesis, the refractory ascites – in 50, the clinical evidences of the chronic portosystemic encephalopathy were present in 29 patients. Splenectomy was performed in 45 patients. The universal influence of splenectomy on the hypersplenism course was observed. However, several complications due to the immunocompetentive organ removing, sharply limit the indices to the splenectomy. At the present time, splenectomy is performed only in patients with the splenogenic liver cirrhosis (Child-Pugh A), where the autoaggressive function of the spleen was confirmed. The syndrome of hypersplenism did not often accompany this condition. At the last time, the embolization of the A. lienalis was applied as the alternative to the splenectomy. The embolization of the A. lienalis was performed in 84 patients (Child-Pugh B – 45, C – 39). The embolization of the trunk type and combined distal parenchymatous was used. In the nearest period after intervention the normalization of leukocytes quantity and increase to the subnormal value of the platelet number in the peripheral blood was observed. The number of erythrocytes and content of hemoglobin essentially did not change. The axis length of the lien reliable decreased, the clinical evidences of the secondary hypersplenism were absent. In the remote period in most patients the moderate asymptomatic cytopenia in the peripheral blood was noted, moreover the platelet number, on the whole, stayed stable, and a leukocytes quantity was decreased. The recurrence of the secondary hypersplenism was revealed in the various terms after operation in 10 patients. In 6 patients it was determined by the recanalization of A. lienalis after truncular proximal embolization, formation of collaterals to the spleen by the left gastrica (2), gastroduodenalis and gastricoepiploica (1) and pancreatic (1) branches. Recanalization was successfully performed in 8 cases.

Blunt liver trauma: retrospective analysis of 25 cases

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Aim: Blunt liver trauma has increased strikingly in the last years, mainly in young patients. Although diagnostic tools and therapeutic solutions are improved, mortality is still high. We analyse retrospectively twenty-five patients with blunt liver trauma observed in our unit in the years 1990–96.
Materials and methods: US and abdominal CT scans were performed only in 17 hemodynamically stable patients. Eight patients were submitted immediately to surgery, with deep hypotension. Surgery was necessary in 14 of 25 patients (56 per cent) to control bleeding with suture, debridement or resection. Multiple organ lesions were present in 68 per cent.
Results: Sensibility of US and CT scan was respectively 88 per cent and 100 per cent. None of the 11 patients treated conservatively died but the overall mortality was 3/25 (12 per cent), all with associated lesions. Uncontrolled haemorrhage (one) and multiple organ failure (two) were the causes of death. These three patients were submitted to surgery being deeply hypotensive. The total surgical mortality was 21·4 per cent (3/14) but raised to 37·5 per cent (3/8) considering only patients operated in a shock state. Postoperative morbidity was 21 per cent and in one patient a liver transplant was necessary for a severe postoperative liver failure.
Conclusions: A conservative approach is possible if the patient is haemodynamically stable, mainly for the reliability of US and CT scan allowing accurate monitoring: about half of the patients could be treated in this way. Associated lesions and deep hypotension before surgery carry a poor prognosis, with a death rate of almost 40 per cent. When it was possible to stabilize the vital signs before surgery, mortality was nil.

Is subtotal cystopericystectomy a safe procedure to treat hydatidic cysts?

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Hepatic infestation of *E. granulosus* is a disease extended through the whole world. Nowadays the only efficient treatment is surgery. All the proposed techniques can be divided in conservative or radical procedures.
Objective: To analyse the morbidity and mortality of subtotal cystopericystectomy (SCP).
Material and methods: In the last 10 years 69 patients with 81 hydatidic cysts have been operated on. Mean age 45 years (range 16–82). Thirty-two cysts had a clear, sterile content. Forty contained bile and 9 were infected. In all cases punction-aspiration of the cyst was performed, injection of hypertonic saline solution (20 per cent) followed by resection of the emergent adventicia, silk suture of the biliar communications and external drainage (12 latex, 57 silicone).

Cholangiography was performed in 35 patients, being necessary a choledocotomy in 7 cases. Cholecystectomy was done in 19 cases. All the patients were treated with antibiotics for a period of 5 days minimum.
Results: Mortality 1/69 due to traumatic rupture of the cyst in a 87 year old patient. Morbidity: 3 biliary fistulas over 7 days resolved after endoscopic papillotomy, 7 intrabdominal abscesses in patients with latex drainages. In 6 times the abscess were treated by CT guided punction. Only 1 patient required open surgery to treat the abscess. Culture results were: 4 *Streptococcus*, 3 *Staphilococcus aureus*. Eleven patients had basal pneumonia. Mean stay 7·2 days (5–21).
Conclusions:
1. SCP is an easy and safe procedure to treat hepatic hydatidic cysts.
2. Close system drainage and antibiotics are necessary to avoid infection of the residual cavity.

Partial pericystectomy vs capitonage in large hepatic echinococcus cysts

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Aim: The aim of this study was to present our experience in the surgical treatment of large hepatic echinococcus cysts. As large cysts were considered those which involved more than three liver segments and had communications with biliary tract.
Patients and methods: In a 10 year period (1981–1990) 130 patients with hydatid cysts surgically were treated; 64 (49·2 per cent) of them had large cysts. Cyst daughters in common bile duct and choledochus were found in 22 (34·5 per cent) of patients with large ones. Female/male ratio was 38 (50·6 per cent) to 26 (47·2 per cent).

Three methods of treatment were used: 1) cystectomy followed by capitonage of cavity (12 patients), 2) cystectomy with total pericystectomy and omentoplication (30 patients), and 3) cystectomy followed by partial pericystectomy, cholecystectomy, exploratory choledochotomy (removal of eventually cysts daughters), T-drainage with intraoperative cholangiography, and omentoplication (22 patients). Saline solution was injected through T tube to identify biliary openings on the cavity surface, and after that smaller openings were carefully sutured, whereas the eroded larger ducts were continually sutured using 5·0 polyglactin 910 (Vicryl).
Results: The perioperative mortality rate was zero. After the analyses and five years ultrasonography follow up of each patient we recorded 13 postoperational biliocutaneal fistulas, one retention of cyst daughter in common bile duct and two recidivation of hepatic cysts. In the groups of patients treated with methods 2 and 3 it was no recidivation nor retention of cysts in biliary tract. The patients treated with second method had longer hospital stay (22·6 days in average).
Conclusions: These results suggest that in the treatment of large hepatic echinococcus cysts (where total pericystectomy is infeasible) the second method had better outcome and it provides better possibilities for early postoperative follow up.

Indications and results of the oesophageal stapled transsection for bleeding varices

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The first choice treatment for haemorrhage from ruptured oesophageal varices is endoscopic injection sclerotherapy. Surgical treatment however may be indicated for recurrent bleeding or inefficient variceal obliteration. This study was performed to assess the efficiency of stapler transsection of the oesophagus to stem the haemorrhage.
Patients and methods: Between 1988 and 1996, 28 patients (aged from 32 to 70 years) have been operated on. Hepatic cirrhosis was the main cause of variceal appearing. Child's hepatic failure evaluation showed stage A in 12 patients and stage B in 16 patients. Emergency indications for the surgical treatment were present in 5 patients, selective indications – in 23 patients.
The operative technique: Consisted of introduction of a stapler device (ILS) by a gastrotomy to the subdiaphragmatical part of the oesophagus. The band was tied around the oesophageal wall upon opened stapler working head. Firing of the device formed a double layer end-to-end anastomosis transsecting and ligating the submucosal varices. When the vagal trunks could not be saved a pyloromytomy was performed.
Results: There were 4 important rebleedings and 2 anastomotic leaks postoperatively. Five patients died, 3 of them were operated on in emergency for massive haemorrhage. After one year 11 variceal relapses were observed.
Conclusions:
1. The surgical treatment should be reserved only for inefficient endoscopic control of life-threatening haemorrhage.
2. The great advantage of stapler transsection of the oesophagus is relative simplicity of use and minor risk of complications.
3. One about 50 per cent of the patients treated by this method remain free of varices one year after the operation.

Technique of interstitial laser therapy (ILP) in our experience

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Locally destroying of colorectal metastases of the liver is an accepted method by ILP. The most promising ILP results are in the treatment of liver metastases, if they are smaller than 3 cm.

The main problem with this method is to monitor tissue changes in real time, and ultrasonography was found to be a little help in this respect. The thermal effects are detectable by high-speed magnetic resonance imaging (MRI) sequences. It can be used to monitor laser-induced tissue changes during therapy, but it is very expensive.

CT, ultrasound or laparoscopic techniques were used to localize the tumours. 19G needles were inserted into the tumour, and through the needle was passed a thin cylindrical diffuser optical fibre. The tumour was heated using low power laser light (2 W) for different time from a Nd:YAG or diode laser, dependant on the tumour size.

New method in human application is thermography to control the thermal effect in real time mode.

With optimal technique, ILP may in the future become a practical, minimally invasive treatment option for patients with colorectal metastases of the liver.

Hepatic resection for benign and malignant liver tumours: experience with 121 consecutive patients

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We performed retrospective analysis of 121 consecutive patients underwent partial liver resection in our department between 1985 and 1997. There were 79 (65·3 per cent) patients with primary tumours: 44 (55·7 per cent) benign and 35 (44·3 per cent) malignant. Metastatic tumours were diagnosed in the remaining 42 (34·7 per cent) cases: 9 (21·4 per cent) synchronic with primary tumour and in 33 (78·6 per cent) cases metachronic. Following resections were performed: segmentectomy in 29 (23·9 per cent) cases, bisegmentectomy in 34 (28·1 per cent), trisegmentectomy in 12 (9·9 per cent), hemihepatectomy in 14 (11·6 per cent) and non-anatomic resections in 32 (26·5 per cent) cases. The benign group consisted of: hemangiomas 19 (43·2 per cent), inflammatory tumours 14 (31·8 per cent), cysts 11 (25 per cent). There were no deaths in postoperative period in patients with benign tumours. We observed: pneumonia in 6 (13·64 per cent), subphrenic abscess in 3 (6·81 per cent), wound infection in 3 (6·81 per cent), biliary fistula in 2 (4·54 per cent) cases. The main reason of metastases was colorectal cancer 71·43 per cent ($n=30$) then gastric cancer 14·29 per cent ($n=6$), biliary duct cancer 7·14 per cent ($n=3$), ovarian cancer 4·76 per cent ($n=2$), idiopatic 2·38 per cent ($n=1$). The mortality rate in the group of 77 patients with malignancy was 10·4 per cent (8 patients). Postoperative complications rates were as follows: pneumonia 14·28 per cent ($n=11$), wound infections 9·09 per cent ($n=9$), biliary fistula 6·49 per cent ($n = 5$), subphrenic abscess 6·49 per cent ($n=5$), acute liver insufficiency 5·19 per cent ($n=4$). Hepatic resection can be a routine procedure in all cases of liver tumours. Intensive care is needed mostly in patients with malignancy.

Complex treatment for liver metastases of colorectal cancer

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Aim: Colorectal cancer is the second frequent cause of death – behind the liver cirrhosis – among the gastrointestinal disorders in Hungary. About 25 per cent of the patients have liver metastases at the time of detection of their colorectal tumour and about at 50 per cent of them have det liver metastases during the course of their disease. Whereas about patients died every year as a consequence of colorectal cancer the nu of those whose liver metastases have not been treated neither with su nor with chemotherapy is very high. We accomplished a retrospe analysis among patients with liver metastases of colorectal cancer h been treated with different methods.

Materials and methods: From January 1982 to December 199 patients had been treated for metastatic colorectal carcinoma. There 43 men and 52 women, the mean age being 55·69 years, ranged 25–79 years. Primary colorectal cancers had all been resected. 85 pa could be classified at the time of the primary resection as Duke's in 10 cases the stage was unknown. We performed in 37 cases a maj 11 cases a minor liver resection, in 11 cases an arteria hepatica can tion, in 7 other cases a vena portae cannula have been simultane implanted for cytostatic therapy. Portal triad occlusion was used in the cases. If the tumour because of its extent or multiplicity could n removed we implanted in 31 patients an arteria hepatica, in 6 patie vena umbilicalis cannula for cytostatic therapy. In 8 cases could on made on exploration. The patients received in the postoperative peri FU and Doxorubicin for cytostatic therapy in every six weeks.

Results: There were no intraoperative deaths in this series. Postope mortality rate was 3·16 per cent. The mean survival was after majo minor surgery 41·4 ($P<0{\cdot}005$) and 25·69 ($P=0{\cdot}0715$) months, wh after implantation arteria hepatica and vena umbilicalis cannula 12·84 and 7·2 month. The mean survival after exploration was onl month.

Conclusions: We have the opinion, that only an aggressive surgery use of adjuvant chemotherapy should prolong the survival of patients ing liver metastasis of colorectal cancer.

Hepatic hydatic cysts: managment with percutaneous draina

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Aim: To investigate the results of percutaneous drainage of hydatid of the liver prospectively.

Patients and methods: One hundred and one patients, with 120 c were treated with percutaneous drainage between October 1994 December 1997.

Results: Of the cysts, 89 were in the right lobe and 31 were in the lobe. Thirty-one patients had been operated for hydatic disease previo All cysts had anechoic or hypoechoic unilocular sonographic appear The mean dimension of the cysts was 7·5±2·9 cm (range 3–10·4 cm). patients received oral 10 mg/kg albendasole perioperatively. After as tion of the cysts under sonographic guidance, they were irrigated wit per cent ethanol. The amount of cyst fluid aspirated and irrigation sol used were 220±75 cc and 175±42 cc, respectively. Four patients devel febrile fever and 3 patients urticaria. The mean hospital stay was 2·1 (range 1–4) days. Patients were followed up 6–39 months. Serial s graphic examinations revealed heterogen echos in cyst cavity (pse tumour). Maximal cyst diameter decreased from 7·5±2·9 cm to 3·2±1· ($P<0{\cdot}001$).

Conclusion: Management of most hydatid cysts of the liver is pos with combination drug therapy and percutaneous drainage.

Our surgical experiences about the hepatic metastases of colorectal tumours

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Aim: Authors evaluate the results of the surgical treatment in case of 24 patients underwent liver resection because of hepatic metastase colorectal tumours.

Patients and methods: Between 1992 and 1997 authors performed liver resection on 24 patients because of the metastasis of colorectal tumour (16 male, 8 female, mean age: 57·6 (32–76). Simultaneous resection of the colon with simultaneous liver operation were performed in 11 cases. In 13 cases hepatic resections were performed at a different time on average 5·9 (1–12) months after the resection of the colorectal tumour. Hepatic metastasis was known at time of the primary operation in 4 cases of them. The surgical method were the following: 6 atypical resections, 7 resections of one hepatic segment, 5 resections of two hepatic segments, 4 hemihepatectomies, 2 lobectomies. In 7 cases multiplex metastasectomy was performed. The average size of the removed tumour was 5·8 (2–18) cm.
Results: There were no mortality in the early postoperative period. Complications were the following: fever (2 patients), transitional elevation of the hepatic enzymes (2 patients), pleuropneumonia (2 patients), TIA (1 patient). There were no surgical complications.
Conclusions: According to our results authors think that the removal of hepatic metastases simultaneously with the removal of the colorectal tumours can be chosen for the elective surgery in cases when the general state of patient allows it. In the case of elder age, other accompanying diseases removing the colon tumour and its liver metastasis is preferable at a different time.

Ultrasound guided aspiration biopsy of focal liver lesions

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Aim: To evalue the diagnostic value of Ultrasound Guided Percutaneous Fine Needle Biopsy (US-FNAB) in diagnosing focal liver lesions.
Materials and methods: During the last 6 years 552 US-FNABs were performed in patients with suspected neoplastic involvement of the liver with 22-gauge Chiba needles, mostly with 'free hand' technique.
Results: Sufficient material for cytological analysis was obtained in 93 per cent of the cases. The biopsies confirmed malignancy in 39·3 per cent, including 14 per cent primary hepatocellular carcinoma. Nine per cent of the cases was suspected of malignancy and in 29·7 per cent benign lesions were diagnosed. Two hundred and thirty-three cases were confirmed histologically and with other follow up methods. The sensitivity rate was 91 per cent, the specificity 100 per cent. There was not any false positive diagnosis and no noteworthy complications were observed.
Conclusion: US-FNAB is a highly reliable, safe, inexpensive diagnostic procedure. Based on our experiences we advise US-FNAB as a routine, first level tool for the diagnosis of focal liver diseases.

Current strategy in the management of hepatic injury

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The presence or suspicion of hepatic injury has traditionally been an indication for surgical exploration. On the other hand, non-operative management is nowadays considered the treatment modality of choice in over 50 per cent of patients with blunt hepatic injuries. The following report analyses retrospectively our experience over the past 5 years.
Patients and methods: The charts of all patients with liver injuries admitted to our hospital during the past 5 years were reviewed. Information collected includes age, sex, mechanism of injury, associated injuries, treatment, complications and outcome. Diagnosis was suspected or proven by either peritoneal lavage or CAT-scan.
Results: Forty patients (m/f: 30/10), with a mean age of 32·7 years, were treated for hepatic injury. Traffic accident was the mechanism of injury in 33 patients, fall of a height in 3, blunt injury in 3 and penetrating trauma in 1 patient. Diagnosis was made by peritoneal lavage in 14 patients, by CAT-scan in 24 and on clinical examination in 2. Isolated liver injury was present in only 4 patients. Twenty-two patients underwent laparotomy (12 simple haemostasis, 6 packing, 3 partial hepatectomy, 1 total hepatectomy awaiting transplantation). In 13 of the 22 operated patients, diagnosis was suspected by peritoneal lavage only. Nine of these patients had associated intra-abdominal lesions that made laparotomy mandatory (6 spleen, 1 kidney, 2 intestinal). Two patients developed a biliary leak, one was treated by endoscopic stenting. Five patients died (22·7 per cent). Mean ICU stay was 12 days. Eighteen patients were treated conservatively. Diagnosis was confirmed by CAT-scan in all of these patients. Four patients had associated intra-abdominal lesions (2 spleen, 2 kidney). One patient developed a haemangioma. No patient died. Mean ICU stay was seven days.
Conclusion: In this series surgery remains the cornerstone in therapy of blunt-abdominal trauma with acceptable morbidity and mortality. Packing is the surgical procedure of choice, while resection and total hepatectomy awaiting transplantation is associated with high mortality. The additional endoscopic stenting of biliary fistula facilitates the postoperative course.

Surgical treatment of the echinococcus cyst in the liver (1991–1997)

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Aim: The aim of this study was to obtain more data about the surgical treatment of echinococcus cysts in the liver. The commonly used techniques are pericystectomy, enucleation, anatomical or atypical resection.
Material and methods: Thirty patients (19 female and 11 male) with liver echinococcus cyst underwent surgical operation between January 1991 and December 1997. Solitaer cyst was removed in 20 cases, duplex cyst in 6 cases. Echinococcus cyst of the liver was resected by a thoracolaparotomy following cystectomy of the left liver lobe of the lung in one patient. The average size of the cysts was 10 cm (5–15 cm). Marsupialization was chosen in 1 case with secondary abscess formation in the cyst, six years ago. We performed single segment resection in 8 cases, double segment resection in 5 cases, three segment were removed in 3 cases. Atypical resection was achieved in 2 cases, pericystectomy in 5 cases, and enucleation in 5 cases. Hemihepatectomy was necessary in 1 case.
Results: One patient died in cardiac failure. Seroma developed in one case. All patients were free of symptoms during their follow-up.
Conclusion: Enucleation or anatomical segment resection of the liver proved to be the best method. We obtained very good experiences with application of the ultrasound dissector.

Benign hepatic tumours: analysis of 19 cases

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Among 93 patients operated in the period 1st January 1992–30th November 1997 for primary liver tumours, we found 19 benign hepatic tumours (48 per cent): 15 hemangiomas, 1 adenoma, 2 hamartoma and 1 focal nodular hyperplasia. Hepatic hemangioma was the most frequent in our series (16 per cent), in 4 cases being located to one segment, in 5 cases extended to 3 segments, 1 case to right lobe and in 5 cases to the left lobe. The preoperative diagnosis was based on the hyperechoic pattern at the ultrasonography and the intense peripheral enhancement after the administration of contrast agent bolus, as well on HPI (hepatic perfusion index) by means of hepatic scintigraphy. The clinical examination found a palpable hepatic mass only in 5 cases – giant hemangioma occurred in 1 case (in this case the surgical exploration demonstrated the definitive diagnosis). The laparotomy was done in all cases: in 10 cases we performed only the exploration and biopsy, in 3 cases left lobectomy, in 1 case left hepatectomy and in 1 case the resection of the quadrant lobe. All patients with hemangioma had a good postoperative outcome, without complications.

One patient presented hepatic adenoma. In this case because the intratumoural bleeding, the preoperative diagnosis suggested cavernous hemangioma. The operation consisted in segmentectomy of the segment IV, the final diagnosis has been demonstrated by the histologic examination of the resected parenchyma.

The hepatic hamartoma was found in two cases, both being operated (hepatic excision – 1 case and left lobectomy – 1 case) and the diagnosis was made after the histologic examination of the resected specimen. One patient with focal nodular hyperplasia was cured by segmentectomy (segment VI) and the postoperative histologic examination pointed the type of the tumour.

In conclusion the heterogeneous appearance of these tumours require surgical exploration and biopsy to avoid the confusion with various malignant hepatic lesions. Finally we discuss the various imaging patterns of the benign hepatic tumours.

Emergency hemihepatectomy and colon resection for septic shock due to diverticultis and hepatic abscess

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A 49-year-old woman was referred to us with the diagnosis of multiple abscesses involving the right liver lobe and severe septicaemia. Intravenous antibiotics and operative insertion of a drain tube into the right liver had not prevented rapid deterioration to a critical condition. Upon arrival, the patient was intubated and depended on high doses of catecholamines to maintain adequate blood pressure readings. Emergency laparotomy revealed diverticulitis of the sigmoid colon with perforation as the cause of the disease. A right side hemihepatectomy and resection of the diseased colon segment were performed with an end colostomy and a Hartmann pouch. The patient could be weaned from the ventilator on the 18th postoperative day. The course was complicated by infected pleural effusions and partial secondary healing of the skin incision.

Conclusion: In this case, emergency hemihepatectomy favourably influenced the course of a septic shock syndrome due to multiple abscess formation in the right liver lobe and a perforation in the sigmoid colon.

Stomach

Marginal ulcer: a series of 40 cases

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Aim: Marginal ulcers are among the most important problems complicating ulcer surgery. Nowadays, except for the complications, arguments still persist about the treatment of marginal ulcers.
Materials and method: In this article, 40 cases with marginal ulcers were examined retrospectively. The type of initial operation, the initial symptoms, the tools to establish the diagnosis, the localization of the ulcer and the treatment approaches were reviewed.
Results: Thirty-one patients (77·5 per cent) were male and 9 (22·5 per cent) were female, all having a mean age of 46·8 years (range: 20–74 years). The initial operations were gastrojejunostomy in 23, gastric resection procedure in 12 and pyloroplasty and vagotomy in 5 of the patients. Twenty patients had come with perforation, 10 patients with bleeding and the remaining 10 patients with gastric stasis. Marginal ulcer was located on the line of anastomosis in 13 patients and distal to the anastomosis in 3 patients. Four patients were urgently operated for haemorrhagic shock secondary to upper gastrointestinal bleeding. The remaining 20 patients had emergency operations for acute abdomen. The mean latency period for the appearance of marginal ulcers was 9·6 years (range: 8 months–25 years). Among the 16 patients with incomplete vagotomy, 2 underwent only complete vagotomy procedure, and among the remaining 14 patients, 7 had primary repair procedure, 4 had transfix sutures, the remaining 3 patients had antrectomy in addition to complete vagotomy procedure.
Conclusion: As a result, incomplete vagotomy might be an important factor for the development of marginal ulcers. Of the treatment options, we are in favour of resection procedures.

Cancer of the stomach in the clinic of surgery at the present time and 25 years ago

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Despite marked advancement in the development of diagnostic techniques, gastric cancer is still diagnosed too late. The aim of the study was comparison of patients operated upon in the Clinic of Surgery at present (in the years 1992–97) and 25 years ago (in the years 1965–70). The number of patients operated for gastric cancer in these two periods of time was similar (100 and 97 patients, respectively), with only a slight increase in their mean age. There was more than a twofold decrease in the number of preoperative misdiagnoses (18 per cent vs 7 per cent) and in the number of patients who underwent only explorative laparotomy (35 vs 14 persons). The number of patients fit for resection procedures rose from 56 per cent to 69 per cent. A threefold rise in the number of radical gastric resections was noted, and this resulted from the widely used stapling techniques.
Conclusions:
1. The above comparison has shown the following:
   - a similar number of operated patients,
   - a persistent high percentage of inoperable cases of gastric cancer and of palliative operations,
   - a threefold increase in the number of performed gastrectomies.
2. The patients present themselves to the surgeon too late despite the development of newly devised diagnostic techniques.

A decline of scheduled gastric surgery?

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Introduction in the last decade of new antiulcerous drugs has brought about a turn in the treatment of chronic peptic ulcer disease which at present is being handed over to the care of the internists. There is an ever increasing number of patients with complications of chronic peptic ulcer.

In the years 1967–1974 – 373 patients (4·9 per cent of all operations) were operated for chronic peptic ulcer. Scheduled operations were performed in 61 per cent and emergency operations in 39 per cent. Median age of the operated patients was 45·5 years, 22 per cent were under 35 years of age, and 4·5 per cent – over 70 years of age.

In the years 1989–1996 – 259 patients were operated for gastric and duodenal ulcer (3·2 per cent of all operations). Sixty-four per cent of them were operated for haemorrhage and perforation, and 36 per cent – because of ineffective conservative therapy. Median age of the operated patients was 55·5 years, 13 per cent of them were under 35 years of age, and 21 per cent – over 70 years of age.
Conclusions:
1. A decrease in the percentage of patients operated for chronic peptic ulcer disease.
2. An almost fivefold increase in the percentage of operated patients over 70 years of age.
3. An almost twofold decline of scheduled operations.

Jejunal pouch after total gastrectomy

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The agastric syndrome after total gastrectomy clinically determinates denutrition and ponderal waste which are always present in acute way in the postoperatory and then in chronic.

These depend on malabsorption and/or quick transit (loss of protein, creatorrhoea, steatorrhoea) or by other (AA) by a drastic reduction of the caloric intake. In absence of neoplastic relapse, the caloric intake can depend by low alimentary capacity with early repletion, dysphagia, oesophagitis, and by alimentary fears.

AA describe the surgical technique performed in six selected patients that had a Roux-en-Y esophagojejunostomy with Hunt-Rodino Pouch and the postoperative results by evaluation nutritional status.

The use of mechanical staplers is very useful. The pouch must not be longer than 16–18 cm to avoid too big dilatation with food residue. However the anastomotic tract from oesophagus to the end of loop must be not less than 40 cm.

Patients were studied by nutritional habits (number of meals, and postprandial disturbances), and by clinical, laboratory, instrumental follow-up: such as protein loss, Vit B12 hoematic concentration and intestinal absorption (Shilling test), xilosuria 24/h, steatorrhoea, glucose tolerance, endoscopy, rx-graphic transit, and emptying time of Pouch by sequential scintigraphy with Tc99.
Results: a) Chronic malabsorption persist in 100 per cent with loss of 350–400 Kcal/die with stool. b) Normal body weight occurred only in four patients (waste inf. 10 per cent). c) Very good protection against biliary reflux, dumping and postprandial disturbances. d) Good reservoir function with gradual food release, the emptying time is like a normal stomach (70–80') if not occurs a bigger dilatation of Pouch (one case).
Conclusions: The increased nutritional capacity does not always mean a greater food intake (maximum 2000–2200 Kal/day), no more a satisfactory physical recovery. The method only satisfies partially the aims however it is a safety intervention recommended only for patients having long life expectation.

Application of the Japanese approach to gastric cancer treatment: does it improve our results?

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Aim: The differences between survival rates in the Western and Eastern countries for gastric cancer have been explained often because a different biological behaviour. Other reasons have also been argued: a better staging system, and a more systematic and aggressive surgical technique, in contrast to a rather pessimistic and nihilistic attitude with this tumour, common among many western well trained surgeons. The aim of this study is to present our results, after applying the Japanese approach to gastric cancer in our hospital.

Methods: From March 1988 to December 1997, 190 gastric cancer patients have been operated in our department. Classification, staging and treatment were performed according to the rules of the Japanese Society for Research of Gastric Cancer (JRSGC) Kaplan–Meier method was applied to survival analysis.

Results: The antrum was the most frequent tumoral location 44 per cent (85/190). Early gastric cancer was diagnosed in 25 cases (13 2 per cent). Patients distribution per stages was· I· 29 (15 per cent), II. 13 (6 per cent), III: 61 (32 per cent) and IV 87 (45 per cent) Elective surgery was performed in 88 per cent (168) of the total number of cases. Total gastrectomy was performed in 88 cases (46 per cent) and subtotal resection in 79 patients (41 per cent). D1 lymphadenectomy was associated in 66 cases, D2 in 86 and D3 in 12. The procedure was defined as absolute curative in 72 cases (38 per cent), relative curative in 35 (18 per cent) and non-curative in 83 (44 per cent). Overall survival after a mean follow-up period of 57 months is 41 per cent After curative surgery the cumulative survival has been 62 per cent, and 5 per cent for non-curative procedures

Conclusion: The Japanese approach to gastric cancer in our experience allows a better staging and prognostic definition of every case, based in clear, objective and realistic criteria

Has lymph node dissection for gastric cancer surgery a therapeutic significance?

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Aim: Although for Japanese authors, lymph node dissection has a definite therapeutic value, it hasn't been until 1994 that western publications have appeared which show and improved survival with extensive dissections vs standard Nevertheless this is still a matter of controversy. The aim of this study is to evaluate in our patients, studied according to the criteria of the Japanese Society for the Research in Gastric Cancer, whether an extended lymph node dissection (D_2/D_3) is associated with an improved survival, or only has contributed to improve staging and a more precise definition of prognosis

Patients and methods: From March 1988 to December 1996, 190 patients have been operated on for gastric adenocarcinoma in our Department. Clinicopathological variables as well as the definitions of surgery were evaluated according with the criteria of the Japanese Research Society for the Study of Gastric Cancer (JSRGC)

Results: The resection rate in our series is 88 per cent (168), with 76 per cent (145) presenting with advanced disease (stages III–IV). Eighty-eight total and 79 subtotal gastrectomies were performed. Lymph node dissection was: D_0· in 4, D_1· in 66, D_2. in 86, and D_3: in 12 patients respectively Postoperative lymph node involvement for resected tumours was. n0 63, n1· 45, n2. 37, n3. 23 patients. Surgery was defined as absolutely curative in 72 (37 per cent), relatively curative in 35 (18 per cent) and no curative in 83 (43 per cent). For patients without lymph node involvement, overall probability of survival with D_1 dissection was 75 per cent vs 65 per cent for D_2–D_3 (no significative). For patients with n1 lymph node involvement, survival with D_1 was 0 per cent, being 63 per cent for D_2–D_3 (P<0·01). With n2 involvement and D_2–D_3, overall survival was 22 per cent

Conclusions: When there is no lymph node involvement, a more extensive lymph node dissection adds nothing in terms of survival, but when there is lymph node involvement, patients' survival improves with a more extensive dissection

Different growth pattern in early gastric cancer-cause of different prognosis?

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Aim: In 1983 Kodama in Japan described different growth pattern in early gastric cancer (penetrating type A and B) and their influence on the prognosis. In Europe, this classification is not applied regularly. Working up our patients suffering from early gastric cancer (EGC), we tried to find out about the influence of the different growth pattern on long-term survival.

Material and methods: From October 1987 to March 1997, 43 patients suffering from early gastric cancer were operated in our department Twenty-two of these were found to have submucosa-type EGC which presented in 13 cases as the more aggressive PEN A type, and in nine cases as the more benign PEN B type.

Results: The histological investigation of the specimen showed positive lymph nodes in two patients of the PEN A group (1×N1, 1×N2) and in one patient of PEN B (N1).

We could follow-up our patients between 6 and 121 months (mean. 51 months). One patient of the PEN A group died in the 28th postoperative month tumour-related, another in the 76th postoperative month from myocardial infarction. One patient of the PEN B group died in the 41st postoperative month from his coronary heart disease

Conclusion: Within our small number of patients we could not prove that the PEN A type is more aggressive. Because of the impressing pathomorphological differences, we consider it necessary to obtain the data of more patients and to follow them up for a longer period of time

Advanced gastric cancer: an emergency hospital experience

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The study tries to establish a clinical and therapeutical attitude for advanced and complicated gastric cancer in an emergency hospital condition taking into consideration the last five years personal experience

Two hundred and forty-eight patients with minimum IIIA Stage disease (International TNBM – 1992) and hospitalized between 1992–1996 were retrospectively analysed.

Complicated cases were noticed: 26·2 per cent (65) – haemorrhage, 6 4 per cent (16) – perforation, 27 per cent (67) – stenosis

Correlation between primary and final diagnosis is discussed upper digestive endoscopy is mandatory (best results over CT-scan, ultrasonography and conventional X-ray)

Preferable surgical interventions were tumour resections even palliative for advanced stages of disease. Postoperative complications had a low rate only 6·4 per cent (16) anastomotic leakage, in-hospital mortality. 6·8 per cent (17)

Our data permitted us to conclude that advanced complicated gastric cancer could benefit aggressive surgery with acceptable results Rapid diagnosis in emergency conditions improved the situation.

The effect of splenectomy on morbidity and survival following gastrectomy for gastric adenocarcinoma

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Aim: We investigated the factors affecting the survival in the patients with gastric adenocarcinoma who underwent gastrectomy and the impact of splenectomy on survival and postoperative infectious complications.

Material and methods: One hundred and nine patients who underwent gastectomy for gastric adenocarcinoma between 1991 and 1997 have been followed up for a mean of 40 months. Twenty-nine (27 per cent) patients were female and 80 (73 per cent) patients were male, with on average age of 59·8 (range 29–87) years Seven patients were in stage I, 27 in stage II, 50 in stage III, 25 in stage IV pathologically. Twenty-nine patients (27 per cent) were node negative. Sixty-one patients (56 per cent) underwent total gastrectomy and 48 patients (44 per cent) underwent distal subtotal gastrectomy Of 109 patients, 44 (40 per cent) underwent splenectomy Chi-square test was used for statistical evaluation Survival curves were calculated using the Kaplan–Meier method

Results: There were no statistical difference between the two groups concerning age, pathologic TNM staging, curability of resection, Borrmann and Lauren classification. However, tumours were statistically larger

(<6 cm vs >6 cm, $P<0{\cdot}05$) and more invasive in the splenectomy group. Postoperative mortality was 13·6 and 7·7 per cent in the patients who underwent gastrectomy with splenectomy and without splenectomy respectively ($P>0{\cdot}05$). Eleven per cent of the patients developed infectious complications in the splenectomy group (3 wound infection, 1 pneumonia, 1 anastomotic leakage) where as infectious complications were encountered in 9 per cent of the patients without splenectomy (2 wound infection, 1 pneumonia, 2 anastomatic leakage, 1 intra-abdominal abscess) ($P>0{\cdot}05$). There was no difference between the survival times of the patients who underwent gastrectomy with curative intent with and without splenectomy respectively in the univariate analysis (mean 24 months vs 32 months, $P>0{\cdot}05$).
Conclusion: The results of this study have shown that postoperative mortality was high in the splenectomy group although this difference did not reach statistical significance. Splenectomy did not affect survival in this series. When the role of spleen on immune system is taken into consideration, it may be better to preserve the spleen unless it is directly invaded by the tumour.

Mortality and risk factors in perforated gastroduodenal ulcers

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Recent data confirm that mortality for perforated gastroduodenal ulcers is high and decreases of it is difficult, because this is not dependent only of the methods of operations use for treatment.

There are same risk factors present at the patients at the moment of operations responsible for high mortality.

We have tried to determine this prognostic risk factors in 3605 patients who between 1 January 1965 and 31 December 1994 are treated for perforated gastroduodenal ulcers at Hospital Center of our University, Military Central Hospital and at six District Hospitals. There are 3495 patients alive (mean years 40±1·6) and 111 dead (mean years 61±2·1) (3·07 per cent). Simple suture have been used at 94·3 per cent of patients, resection 3·16 per cent, truncal vagotomy 2·35 per cent and unoperated 0·16 percent.

This study based on statistical analysis, (chi square testing) showed the following range of risk factors responsible for mortality:

– Age	$P\leq0{\cdot}001$
– Time from perforation to surgery over 24 hours	$P\leq0{\cdot}001$
– Advanced peritonitis	$P\leq0{\cdot}001$
– Shock	$P\leq0{\cdot}001$
– Concomitant diseases	$P\leq0{\cdot}001$
– Concomitant haemorrhages	$P\leq0{\cdot}001$
– Ulcer localizations	$P\leq0{\cdot}001$
– Ulcer history over 3 months	$P\leq0{\cdot}001$
– Gender	$P\leq0{\cdot}05$

Autoexpandable stent as palliation of obstructive antral carcinoma

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Autoexpandable stents have previously been used in arterial, biliary, oesophageal and colonic stenosis. We introduce a new possibility of the procedure, such as palliation of a malignant, unresectable stenosis of the gastric outlet.
Case report: Seventy-three year old male with extensive adenocarcinoma of the gastric antrum. At operation (19th July 1997), the tumour was extended to transverse mesocolon, mesenteric axis and pancreas, with implants over the great omentum. Thus, it was considered unresectable and the laparotomy limited to biopsies. The patient was admitted 4 months later showing profuse vomiting and inability for oral feeding. On endoscopy the gastric antral malignant stenosis had become complete, preventing the passage of the gastroscope. Using a combined gastroscopic and radiological aid in an ambulatory setting, an autoexpandable stent was placed along the stenosis (12 December 1996), with immediate restoration of gastroduodenal transit as it was showed by the radiopaque contrast passage. The patient reassumed oral feeding 5 hours after the procedure, and was discharged in less than 24 hours. In the first month the patient returned to normal oral feeding and had 7 kg weight increase. Five months after the procedure the tumour had grown through the stent and restenosed the gastric outlet. A new autoexpandable stent was placed inside the first (12 July 1997) with resolution of the gastric obstruction. However, the patient died one week after due to massive mesenteric thrombosis.
Discussion: The placement of an autoexpandable stent to palliate the unresectable malignant gastric obstruction provided 6 months of good quality of life survival. Other alternatives would have been gastro-enterostomy or feeding jejunostomy. Both procedures require surgical intervention. In the case of gastro-enterostomy the bulky antral mass would have forced a high placement of the anastomosis in the gastric wall, thus impairing gastric emptying. Feeding jejunostomy is psychologically bad tolerated by patients, and gastro-esophageal and saliva regurgitation are not prevented.
Conclusion: The autoexpandable stent placed endoscopically is an excellent palliation for unresectable malignant stenosis of the gastric outlet. The procedure presents advantages over the surgical alternatives, as simplicity, avoidance of anaesthesia and laparotomy, ambulatory setting and excellent functional results.

The correction of endotoxicosis at stages of treatment of children with acute pathology of abdomen

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The purpose of the study was to optimise correction of endotoxicosis at various stages of treatment of children with acute abdominal illnesses. We investigated and compared the results of complex treatment of 40 patients with generalized appendicular peritonitis (28), adhesion obstruction (8) and intestinal intussusception (4). Twenty children received routine therapy at various stages of treatment. In a second group of 20 patients, the preoperative preparation included a session of haemofiltration of 1·5–2 times the volume. Concentration of markers of oxidative stress sharply rose in patients of the first group 3 hours after operation, corresponding to endotoxicosis IV degree. Dien conjugations reached 9·2 standard units and above, malon dialdchide (MDA) – 14·0 mgmol/g of fibre; peroxide haemolysis of erythrocytes – 25·0 per cent; middle molecules – more than 0·430 standard units of optical density. In contrast, in the second group 3 hours after operation the parameters of endotoxicosis corresponded to II degree. Peroxide haemolysis of erythrocytes fell to 15·0 per cent and below, MDA-less than 10·0 mkmol/g of fibre; dien conjuation – was less than 4·4 standard units; middle molecules – less than 0·75 standard units of optical density. Postoperative complications occurred in 12 patients of the first group (early obstruction, anastomotic leakage, progressive peritonitis and intestinal fistula). Postoperative complications were observed in 7 patients in the second group. There were no intestinal fistulas we conclude that haemosorption is a method of choice of preoperative preparation of patients with complicated severe abdominal pathology. Plasmapheresis is a method of choice in the early postoperative period. Haemosorption and xenoperfusion are helpful in some cases.

Value of panendoscopy associated with laparoscopy in the detection of stomach cancer

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Lesions developing in submucous and muscular membrane of the stomach are extremely difficult to detect without the use of gastrofiberoscope with ultrasound detector.

The aim of the present study is to estimate the diagnostic value of panendoscopy associated with laparoscopy in the detection of the lesions of stomach and duodenum wall, especially those situated in submucous and muscular membrane, which are not accessible by means of conventional panendoscopy

Examination was performed after the laparoscopic cholecystectomy. Intraoperative panendoscopy was used. Stomach wall was examined first in the light of the fiberoscope and then of the laparoscope

Examination was performed in 26 randomly chosen patients The front wall, major and minor curve of the stomach, and the front wall of the duodenum was observed Seven cases of gastric or duodenal erosions and two cases of post-ulcus scars were discovered. In the places where the lesions were located, the change in the intensity of penetrating light was observed It was noted that the vascular net is more abundant in the vicinity of the lesions. The smallest lesion detected during the examination was 2 mm long. The examination together with video-recording and taking photos of the lesions lasted from 10 to 15 minutes There were no complications connected with the examination recorded

An associated panendoscopic and laparoscopic examination enables the assessment of the wall structure of the examined organ. Therefore it is possible to detect very small lesions, to estimate their range and take material for histopathological examination.

Gastric stump cancer – a review of 21 cases

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Aim: The gastric stump cancer is a pathologically rare entity that a malignant neoplasia appears in a stomach operated on with benign pathology This study was performed to identify the anatomo-clinical characteristics of this tumour and analysed the overall 5-year survival in these patients.
Patients and methods: From January 1974 to December 1995, 1339 patients with gastric cancer were operated on in our Institution, of which 21 (1·6 per cent) had gastric stump cancer All cases were analysed retrospectively Results of the survival and latency analyses were displayed graphically using the life-table method. The mean survival was 13 months and the mean follow-up was 17 months (range 2–72 months).
Results: Nineteen patients (90·5 per cent) were men and 2 (9 5 per cent) were women, with an average age of 63 8±8·8 years (range 50–79 years). The mean time of presenting complaints was 7·9±6·7 months and the most common complaints were epigastric pain and postprandial fullness (66 per cent) followed by anorexia/loss weight (38 per cent) and by vomiting/regurgitation (28 per cent). The mean time between the first surgery and the tumour development was 27·5 years (range 10–45 years) In 20 (95·2 per cent) patients, the diagnosis was performed with endoscopic study and confirmed by biopsy. Curative resection (R0) was performed in 13 (62 per cent) patients, 2 (9·5 per cent) had palliative surgery (R1 or R2) and 6 (28·5 per cent) had exploratory laparotomy or by-pass. Nine (42 8 per cent) tumours were macroscopically vegetative, 5 (23·8 per cent) ulcerative and 3 (14·3 per cent) infiltiative On the histological study, 3 (14·3 per cent) tumours were well differentiated (G1), 8 (38 per cent) moderately (G2) and 3 (14·3 per cent) poorly differentiated (G3). In TNM classification (UICC), 5 (24 per cent) patients belonged to stage I, 2 (10 per cent) to stage II, 5 (24 per cent) to stage III and 9 (42 per cent) to stage IV Eight (38 per cent) patients were submitted to complementary treatment with chemotherapy. The curability rate was 62 per cent and the resectability tumour rate was 71 per cent Four (19 per cent) patients had postoperative complications (1 intraabdominal abscess, 1 pulmonary infection, 1 acute pancreatitis and 1 acute pancreatitis with pulmonary infection). The average length of hospital stay was 15 days. The overall 5-year survival rate was 33 per cent
Conclusions: The gastric stump cancer is a neoplasia, which showed a male preponderance In our series the mean time between the first gastric surgery and the tumour development was 27·5 years These results support the need of strict endoscopic follow-up of these patients 10–15 years after the first surgery and by this way identify the tumour in a precocious stage.

Risk factors for surgical treatment of gastric cancer with D2 dissection, Turkish experience

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Gastric cancer is one of the most important problems in Turkey and will be the leading one in cancer deaths. The aim of this report is to discuss the results and the risk factors that effect the morbidity and mortality rates in patients having D_2 dissection in Gastric Cancer Study Group of Ankara University Faculty of Medicine, Surgical Oncology Department

The results of 300 patients were discussed who underwent surgical treatment between January 1991 and December 1996. D_2 dissection was performed routinely. Two hundred and thirty-five patients were treated with curative intent and 65 were palliative. Median age was 62 (22–75), (59 per cent) 177 of 300 patients were male.

Duration of operation, blood transfusion, age, type of gastric resection, pancreatectomy, splenectomy and other combined resections were evaluated by multivariate analysis. Hospital deaths were 7 per cent and overall complications were 28·2 per cent Age and anastomosis leakage was the most important, pancreatectomy was significant risk for hospital deaths Survival rates were tested by Kaplan–Meier test and 3-year survival rates were 65 per cent. TNM Stage, lymphatic invasion, perineural invasion, diameter of primary tumour, extension in gastric wall, number of metastatic lymph nodes and splenectomy were important risk factors for survival

Although surgical treatment of gastric cancer has shown increased rates of morbidity and mortality in patients having D_2 resection, according to our experience extended lymph node dissection is more effective modality for local control and survival.

Cancer of the stomach – does it still remain a diagnostic and surgical problem?

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Gastric cancer ranks among malignant tumours that are diagnosed too late The effectiveness of its treatment is still poor. In the present study an attempt has been made to find out about the cause of this situation. The analysis was conducted of 121 patients, 74 males and 47 females aged from 32 to 83 years, operated upon for gastric cancer in the Clinic of Surgery in the years 1988–97 (1·1 per cent of all persons operated during this period of time). Under 50 years of age were 10 per cent of them, and over 70 yr – 38 per cent. Their history length and preoperative symptoms were assessed The discussed 10-year space of time was divided into two 5-year periods, and in each comparison was made between the diagnostic findings obtained and the kinds of surgery performed. Age proportions of the operated persons were almost unchanged. In the years 1988–92 inoperable gastric cancer occurred in 44 per cent of cases, and in the years 1993–97 in 28 per cent of cases. An almost twofold increase in the number of resection procedures (27 per cent to 48 per cent) was noted.

Conclusions:

1 The diagnostic investigations in gastric cancer are performed too late despite the early appearance of the first symptoms.

2 In a considerable number of patients the disease runs an asymptomatic course.

3. During the last 5 years a rise in the percentage of resection procedures among the patients studied was observed.

Results of surgical treatment in proximal and distal gastric cancer

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A retrospective study was performed on 468 consecutive patients operated between 1985 and 1997 in our department with gastric cancer Comparison of material and results was done due to localization in prox-

imal (PPS) and distal (DPS) part of the stomach. There were 210 (44·9 per cent) patients in PPS and 258 (55·1 per cent) in DPS group. In women localization was more often in distal part with significant difference $P<0·001$ [PPS: nM=161 (76·7 per cent), nF=49 (23·3 per cent); DPS: nM=159 (61·6 per cent), nF=99 (38·4 per cent)]. Patients in PPS were significantly younger than in DPS group – $P<0·005$ (PPS-56(13); DPS-60(11)).
Resections: PPS n=157 (74·8 per cent), DPS n=214 (82·9 per cent) $P<0·05$; between them curative: PPS n=52 (33·1 per cent), DPS n=96 (44·8 per cent) $P<0·01$. This difference was significantly accompanied with appearance of stage IIIb and IV (WHO classification) in both groups: PPS n=161 (76·7 per cent) and DPS n=162 (62·8 per cent) ($P<0·005$).
Early results: 37 (17·6 per cent) patients died in PPS and 28 (10·9 per cent) in DPS group ($P<0·05$). 5-year survival rate – among curative restrictions – in PPS group was 36·5 per cent and in DPS 53·1 per cent ($P<0·05$).
Conclusions: Epidemiological differences and bad prognosis in PPS group suggest that new treatment protocols should be designed to include the location of the neoplasm.

Palliative resection of cardia cancer with mechanical and manual reconstruction of digestive tract in our department

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We performed retrospective analysis of 105 consecutive patients with cardia cancer underwent palliative resection in our department between 1985 and 1997. Two groups of patients with different type of anastomosis sutures were compared: mechanical 78 (74·3 per cent) and manual 27 (25·7 per cent). There were no significant differences in sex, age, duration of symptoms, weight loss, size of the tumour, neoplastic infiltration, metastases and in the histopathological examination. In the mechanical group all patients were operated by opening abdomen cavity. Mean duration of operating procedure in this group was 230±58 min ($P<0·005$). The most dangerous postoperative complication – anastomotic leakage was noted in 2 (2·56 per cent) patients. Mortality reach 11·5 per cent (n=9) in early postoperative period, death caused by pulmonary insufficiency was noted in 3 (3·84 per cent; $P<0·05$) cases. In the second group during the operation procedure have had to perform also thoracotomy in 15 (55·5 per cent) cases ($P<0·001$). The procedure was longer 290±93 min ($P<0·005$). The main postoperative complication – anastomotic leakage was observed in 2 (7·4 per cent) cases. Mortality rate was on the level of 33·3 per cent (n=9) in early postoperative period and the pulmonary insufficiency deaths were more frequent 6 (22·2 per cent; $P<0·05$) patients. Mechanical staples should be used because of the shorter operation time and advantage of abdominal cardiectomy. We did not observe significant difference in anastomotic leakage between both groups of patients.

Reliability of preoperative staging of gastric adenocarcinoma by imaging techniques

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Aim: Ultrasonography (US) and computerized tomography (CT) are the most and frequently used imaging methods to determine the extent of gastric adenocarcinoma preoperatively. In this study the reliability of preoperative staging with US and CT was assessed in the patients with gastric adenocarcinoma.
Material and method: The difference between the preoperative and pathological staging were studied in 132 patients who underwent laparotomy for gastric adenocarcinoma between 1991–1997. Thirty-five patients (27 per cent) were female and 97 (73 per cent) were male. Seven patients were in stage I, 27 in stage II, 50 in stage III, 48 in stage IV pathologically. Twenty-eight patients had peritoneal metastasis and 29 patients had liver metastasis. Statistical analysis was done by using chi-square test.
Results: In preoperative evaluation, there were 32 patients in stage I, 59 patients in stage II, 17 patients in stage III and 24 patients in stage IV. However, in pathological evaluation there were 7 patients in stage I, 27 patients in stage II, 50 patients in stage III and 48 patients in stage IV. The patients were found to be understaged by clinical evaluation when compared with pathological assessment ($P<0·0001$). The sensitivity, specificity and accuracy of US and CT were shown in Table 1.

	Peritoneal metastasis		Liver metastasis	
	US	CT	US	CT
Sensitivity	8	15	77	76
Specificity	100	100	95	100
Accuracy	80	77	95	93

Conclusion: These findings showed that patients were falsely understaged with preoperative staging probably because of the inaccuracy of US and CT in demonstrating peritoneal metastasis.

The effect of resection type on mortality and morbidity in gastric adenocarcinoma

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Aim: In this study, we compared total gastrectomy (TG) with distal subtotal gastrectomy (DSG) concerning postoperative morbidity and mortality.
Material and methods: Between 1991–1997, 61 patients underwent TG and 48 patients DSG because of gastric carcinoma. Mean follow-up time 40 months. Twenty-nine (27 per cent) patients were female and 80 (73 per cent) were male, with an average age of 59·8 years (range 29–87). In TG group, 2 patients were in stage I, 15 in stage II, 29 in stage III, 15 in stage IV, in DSG group, 5 patients were in stage I, 12 in stage II, 23 in stage III and 10 in stage IV pathologically. Four patients in TG group and 3 patients in DSG group underwent emergency laparotomy because of tumour perforation in three patients and tumour bleeding in four patients. In TG group Roux-en-Y oesophagojejunostomy, in DSG group Billroth II gastrojejunostomy reconstruction types were preferred. All anastomoses in both groups were performed manually. The tumour was in middle third in 8 and lower third in 40 patients in DSG group and 19 in upper third, 28 in middle third, 4 in lower third of the stomach in TG group. Splenectomy was performed in 40 patients in TG and in 4 patients in DSG group. Chi-square test was used for statistical evaluation.
Results: There were no statistical difference between the groups concerning age, curability of operation, tumour differentiation, tumour size, pathologic TNM staging. The 4-year cumulative survival rates were 4 per cent and 5 per cent in TG and DSG groups respectively. The mean number of removed lymph nodes was 12 in DSG group and 20 in TG groups ($P<0·05$). The mean number of metastatic lymph nodes was 5·2 in DSG group and 9 in TG group ($P=0·09$). No statistical difference was found between DSG and TG groups concerning perioperative blood transfusion (46 per cent vs 58 per cent), anastomotic leakage (0 per cent vs 5 per cent) and postoperative mortality (6 per cent vs 13 per cent).
Conclusions: Although postoperative complication and mortality rates were slightly higher in total gastrectomy group than in distal subtotal gastrectomy group this difference did not reach statistical significance. The results of this study have revealed that TG can be performed with an acceptable mortality and morbidity rates when compared with DSG in the treatment of gastric adenocarcinoma.

Useful and useless diagnostic procedures in oesophageal cancer

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Aim: After confirming the diagnosis of oesophageal cancer by endoscopy and biopsy all further diagnostic measures are initiated to clarify general operability and surgical resectability in particular.

The decision whether to introduce any neoadjuvant treatment and its follow-up examinations are based on preoperative staging procedures, too.

Finally the surgical approach is chosen according to the localization and extension of the tumour established by those imaging techniques.

Materials and methods: Analysing data of 150 patients with cancer of the esophagus who were treated in our department from January 1987 until April 1997 the validity of the various examinations are interpreted.

Results: In 35 patients the tumour was not resected (resection rate: 77 per cent). This could be referred to additional informations obtained by thoracic and abdominal CT-scan in only four cases. In total the results of CT-scans lead to consequences for the further treatment in 15 per cent (22/150).

Endoluminal ultrasound was performed in 60 patients since 1993. Compared to the postoperative histopathological classification the T-stage was correctly assessed in 50 per cent (23/46: in 14 patients there was no histopathological matching available) whereas metastatic lymph node enlargement was detected in 65 per cent (27/46).

In tumours of the proximal and middle third bronchoscopy was employed to rule out any infiltration of the tracheobrochial system which then was found in 8 patients out of 30 (24 per cent) who did not undergo resection.

If it was possible to pass the tumour stenosis by endoscope, in 86 per cent (83/96) any additional diagnostic procedure did not interfere with the treatment.

Conclusion: Due to limited logistic and financial sources the routinous use of especially technical techniques for preoperative staging in oesophageal cancer should be reevaluated.

Transhiatal oesophagectomy: management of intraoperative complications

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Transhiatal Oesophagectomy (THO) intraoperative complications are rare but serious. The aim of this retrospective study is to assess the rate and the type of THE intraoperative complications without thoracotomy.

Material and methods: From 1986 until 19976, 270 THO were consecutively performed either for carcinoma of the oesophagus (200), benign disease of the oesophagus (n=30), or for other disease (n=40). The technique includes constant opening of the pleura, therefore pneumothorax is not a complication.

Results: Complications occurred in 5 cases (1·8 per cent) and were of two types: vascular (2) and tracheal (3). All of these complications were diagnosed peroperatively.

Vascular wounds were diagnosed in view of massive bleeding. In the first case it was venous bleeding, a right anterolateral thoracotomy was immediately performed allowing suture and hemostasis of an azygos vein wound. In the second case bleeding was uncontrolled, haemodynamic failure occurred. An immediate left anterior thoracotomy was performed. Bleeding came from an aortic branch wound which was immediately sutured allowing good hemostasis.

Three tracheal lacerations occurred during blunt dissection. One, involving the high membranous trachea was sutured through a partial upper sternal split. The second involved the membranous carina: THO was completed with retro sternal by-pass. Then, changing the selective ventilation to the left main bronchus, a right postero lateral thoracotomy was performed and tracheal suture done. The third involved cervical trachea and was sutured through the cervical incision. Concerning tracheal complications, two of them resulted from overinflated tracheal cuff and the third occurred after difficult intubation. In these three cases, postoperative artificial ventilation was shorter (less than 48 hours) to avoid high pressure on the tracheal sutures.

Among these 5 patients, one had postoperative pneumonia. No other complications occurred. None of these 5 patients died.

Conclusion: Intraoperative complications occurring during THO are rare (1·8 per cent) but serious. They require urgent management by thoracic approach.

Therefore, solid experience in thoracic surgery is needed to perform THO safely.

Oesophageal motility after modified Sugiura procedure

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Aim: Evaluation of oesophageal motility in cirrhotic patients with esophageal varices subjected to modified Sugiura procedure.

Material: Extensive gastro-esophageal devascularization and oesophageal transection is the method of choice in treatment of bleeding oesophageal varices after failure of sclerotherapy. It ensures control of variceal bleeding without loss of hepatic portal perfusion. Nevertheless such an extensive operation raises the question of its influence on oesophageal motility. It is also controversial how does acid reflux affect the varices and what role does it play in initializing variceal haemorrhage. Thirty-seven patients with hepatic cirrhosis and oesophageal varices were evaluated for gastro-oesophageal reflux and oesophageal motility disorders. Standard 24-hour pH-metry, and combined 24-hour pH and manometry were used. Preoperative pH values confirmed reflux in 58 per cent of patients. They did not differ significantly after the operation. Twenty-four-hour manometry showed significant degree of peristaltic dysfunction, in the form of insufficient and 'dropped' peristaltic sequences. On the other hand, contractile action in the distal oesophagus showed proper manometric values. All analysed parameters also did not differ significantly before and after the operation.

Conclusions: In our material gastro-oesophageal reflux occurred in 58 per cent of cirrhotic patients. Manometric measurements confirmed impaired motoric function in cirrhotic patients with varices. The results did not differ significantly after oesophageal transection. Data obtained from 24-hour pH-metry suggest, that the operation did not cause significant increase of G-E reflux.

Palliation of inoperable oesophageal carcinoma treated by self-expanding stents

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Introduction: Less than 40 per cent of oesophageal carcinoma can be treated with conventional curative surgical procedures. Dysphagia is the main complaint of these patients, even in 20 per cent of curative surgically resected patients. Endoscopic laser therapy (ELT) and self-expanding stents (SES) are used for palliation. ELT has the lowest rate of complications but the dysphagia-free interval does not last longer than for 4–6 weeks. SES have been shown to be superior to conventional rigid plastic endoprostheses allowing a large self-expanding diameter and a rapid palliation of symptoms.

Aim: To evaluate our experience in the treatment of inoperable oesophageal carcinoma using metallic self-expanding stents.

Patients and methods: This is a retrospective study of the SES placed for palliation of malignant oesophageal strictures. Since January '93 until March '97, 80 SES were placed in 78 patients (mean age: 60·6 years, range: 34–85; 70 males and 8 females). Inclusion criteria were: 1) Locally advanced disease; 2) Systemic disseminated disease (M1); 3) Poor general conditions, and 4) Patients who rejected surgery. Covered stents (Wallstent, Gianturco-Rosch, Strecker) and non-covered stents (Strecker, Wallstent) were used. Twenty-two per cent of patients received neoadjuvant radiotherapy and 35 per cent chemotherapy plus radiotherapy. Dysphagia score was used for palliation criteria. patients were evaluated every month until death.

Results:

Dysphagia score	0	1	2	3	4
Pretreatment dysphagia (%)			8·7	31·3	60
Posttreatment dysphagia (%)	64·6	30·4	5		

Data presented as percentage of patients.

Fifty patients had oesophageal adenocarcinoma and 28 sqamous cell carcinoma. There were no differences in the palliation according to pathological findings or location of the stricture. 76·7 per cent had a stricture at the upper or medium oesophagus and 23·3 per cent at the lower oesophagus. 97·9 of the SES were successfully inserted but 6 per cent of them needed to be replaced. Six per cent had to be dilated with balloon catheter. Placement complications were bleeding (9·09 per cent), chest pain (29·2 per cent). Long term complications were recurrent dysphagia (35·4 per cent), migration (5·3 per cent), tumour ingrowth (46·4 per cent), tumour overgrowth (4 per cent), food-bolus impaction (7·7 per cent). Mean duration of hospitalizatrion were 4·9±1·2 days. Mean survival time were 125·5 days.

Conclusions: SES can be used safely for dysphagia palliation in cases of unresectable esophageal carcinoma.

Coated vs uncoated self expanding stents in the treatment of malignant oesophageal strictures

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Background: Esophageal obstruction due to cancer can produce debilitating symptoms such as dysphagia and aspiration pneumonia. Obstruction could be caused by esophageal and bronchial tumours infiltrating mediastinum. Laser therapy is not always indicated in cases of extrinsic compression, requires repeated sessions and is not free of complications. Oesophageal prosthesis (SES) can easily relieve the symptoms allowing oral feeding for a long time. Uncoated self-expanding stents (USES) have been used for dysphagia palliation for a long time, but tumour ingrowth can prevent for a complete dysphagia relieve. Coated self expanding stents (CSES) were developed to avoid tumour growth inside the lumen allowing a longer symptom free interval.

Aim: This is a comparative study between the USES and CSES in the palliative treatment of malignant oesophageal strictures. Retrospective study.

Material and methods: Since January '93 until March '97, 101 SES were placed in 99 patients (mean age: 60·6 years, ranged: 34–85; 70 males and 8 females). Inclusion criteria were: 1) Locally advanced disease; 2) Systemic disseminated disease (M1); 3) Poor general conditions, and 4) Patients who rejectes surgery. Covered stents (Wallstent, Gianturco-Rosch, Strecker) were used in 27 patients (27·2 per cent) and non-covered stents (Strecker, Wallstent) were used in 72 patients (72·7 per cent). All endoprostheses were deployed successfully in the desired location but two needed balloon dilation. Visick Dysphagia score was used for palliation criteria. Patients were evaluated every month until death.

Results:

	Histological type				Location			
Stent type	Squamous	Adeno-carcinoma	Bronchial carcinoma	Others	Upper	Middle	Lower	Associated fistula
CSES	14	6	6	1	12	10	5	16
USES	42	16	13	1	37	17	18	1

Data presented as percentage of patients.

Eight patients in the USES groups had a complication (migration $n=3$, toracic pain $n=1$, bleeding $n=2$, obstruction $n=2$) and only one patient in the CSES group (bleeding). Dysphagia improved in all but one patient in the CSES group and in all but 5 patients in the USES group, moderate dysphagia appeared in 2 patients in the CSES group and in 38 patients in the USES group. One patient died at the 14th postoperative day because of aorta-oesophagus fistula due to migration of the prostheses.

Conclusion: Both CSES and USES are useful in the treatment of inoperable malignant stenosis of the oesophagus. Both prostheses can be safely placed with a low rate of complications. CSES seem to be superior to USES in the long-term relief of dysphagia.

The value of surgery in oesophageal perforations

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Introduction: The aim of our study was to evaluate effectivity of the surgical treatment for oesophageal perforation caused by various incidents.

Patients: Between 1991 and 1996, 11 patients with perforation of the oesophagus were treated in the department. The mean age was 54 years (range 24–68); 4 patients were female. The perforation was located in the cervical part of the oesophagus in 5 cases, and in the thoracic part in 6 cases. Blunt neck trauma in 1 case, foreign body and accidental intubation in 2 cases each had led to perforation of the cervical oesophagus. The aetiology of the intrathoracal oesophageal perforation was Boerhaave's syndrome in 3 cases, iatrogenic in 2 cases, and Barret ulcer perforation in 1 case.

Results: The treatment for cervical oesophageal perforation consisted of antibiotics, nasogastric tube or gastrostomy, total parenteal nutrition, and surgical suction drainage. All 5 cases recovered completely. In the cases of intrathoracal oesophageal perforation, within 24 h of the onset, the surgical treatment was suction drainage and primary closure of the leakage with gastrostomy (3 patients). Three patients presented late (>24 h after the incident). In these cases, the surgical treatment consisted of oesophagectomy, cervical oesophagostomy, mediastinal drainage and feeding gastrostomy. In spite of aggressive surgical treatment, one patient died due to mediastinitis and severe sepsis. In the remaining 2 cases, the alimentary tract was reconstructed with ileocolon.

Conclusions: The prognosis of oesophageal perforation depends essentially on the perforation site and the time of diagnosis. Cervical oesophageal perforation responds well to surgical treatment. In intrathoracal oesophageal perforations primary reconstruction is suggested only after an early diagnosis. After 24 hours of the onset resectional surgery has given good results for intrathoracic oesophageal perforation.

Thorascopic assisted transhiatal oesophagectomy – new lamps for old?

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Surgical excision remains the best chance of long-term survival for patients with oesophageal carcinoma. The advent of minimal access surgery allows accurate dissection and thorascopic mobilization of the oesophagus without the need for thoracotomy and its associated complications. We report our experience of thorascopic-assisted transhiatal oesophagectomy (TATH) between December 1993 and June 1996. Forty-two consecutive patients underwent TATH. Twelve patients required conversion to thoracotomy because of pulmonary adhesions, size of tumour, tracheal injuries or ventilation difficulties. The mean age of the patients was 65·7 (45–80) years. The stricture length was between 3–11 cm in the TATH and 5–12 cm in the conversion group. Average total operation time was 308 minutes (235–400) in the TATH, thoracoscopic dissection taking 83 minutes (50–120). One death occurred in each group. The mean postoperative hospital stay was 14 days in both groups. The 1 and 2 year survival rates were 71 per cent (30 of 42) and 60 per cent (25 of 42) respectively. The results of TATH are very similar to those of conventional surgery. We propose that TATH may offer an advantage in terms of visualization of mediastinal structures during dissection, thus minimizing operative complications.

Pulmonary complications following transhiatal oesophagectomy in patients with severe chronic obstructive pulmonary disease

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Transhiatal esophagectomy (THE) was proposed in order to reduce the incidence and the severity of postoperative pulmonary complications (PC). Certain surgical teams reserved THE for patients who are unsuitable for a transthoracic oesophagectomy, notably when there coexists a severe chronic obstructive pulmonary disease. The aim of this study is to assess this approach by evaluating the influence of preoperative pulmonary function on the pulmonary morbidity and mortality following THE.

Material and methods: From 1986 to 1994, 136 THE were consecutively performed for carcinoma of oesophagus. There was 111 men and 25 women with a mean age of 60 years (range 36 to 91). The patients were divided into two groups: those with a forced expiratory volume in one second (FEV) lower than 60 per cent of the theoretical value (*n*=19), indicating severe chronic obstructive pulmonary disease and those with a FEV higher than 60 per cent of the theoretical value (*n*=117). A major PC was defined as requiring initial assisted ventilation higher of more than 48 hours or requiring endotracheal reintubation for a respiratory failure. The other PCs were considered minor.

Results: PC occurred in 36 patients (26 per cent). The respiratory mortality rate was 3 per cent (*n*=4). Comparison of the two groups showed:

	IC stay	Total PC	Minor PC	Major PC	Respiratory mortality
FEV >60%	8·0±4·2	25% (*n*=29)	18% (*n*=20)	8% (*n*=9)	1·6% (*n*=2)
FEV <60%	9·3±11·6	36% (*n*=7)	14% (*n*=3)	21% (*n*=4)	10% (*n*=2)
P value	0·067 (n.s.)	0·31 (n.s.)	0·78 (n.s.)	0·05 (s)	0·094 (n.s.)

Conclusions: Severe chronic obstructive pulmonary disease did not significantly increase pulmonary morbidity rate following THE.

However, PC occurring in this group of patients appeared more severe with a significant increase in major PC and respiratory mortality rates.

CYFRA 21-1 – its implication as a prognostic factor for the squamous carcinoma of the esophagus

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Introduction: Up to now there is no reliable tumour marker for malignant diseases of the oesophagus. Some studies from the last three years indicate the role of the marker CYFRA 21-1 as a prognostic factor in squamous lung cancer.

Aim: Evaluation of the role of CYFRA 21-1 as a prognostic marker for the squamous cell carcinoma of the esophagus.

Patients and methods: Sera of 35 patients suffering from squamous cell carcinoma of the esophagus were examined in a prospective trial. Blood examinations were made before surgery and during the follow-up one year after the operation. Statistcal analysis was done using the one sample t-test.

Results: The concentration of CYFRA 21-1 showed significant correlation to the local tumour growth. The mean concentration was 1·29 ng/ml in case of early cancer of the oesophagus (*n*=6), 1·50 ng/ml [T2, *n*=9], 2·07 ng/ml [T3, *n*=16] and 2·43 ng/ml [T4, *n*=3]. There was no statistical significance in substance concentration with regard to the nodal status or in case of distant metastases.

Conclusion: CYFRA 21-1 is a useful marker indicating the extent of local tumour growth but fails to indicate lymph node metastases and distant metastases in squamous oesophageal cancer.

Transoral application of EEA stapler after subtotal oesophagectomy

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The authors describe successful usage of EEA Stapler for reconstruction after subtotal oesophagectomy for spinocellular carcinoma in middle third and in distal third of oesophagus in two patients. In both cases EEA stapler was applicated *transoral and made oesophagogastric anastomosis.* We had no complications pre- or postoperatively. Patients left clinic on 14th or 21st day after operations. Authors consider transoral application of EEA stapler to be good alternative for cervical oesophagogastric anastomosis after subtotal oesophagectomy.

Mortality of patients after resection for oesophagus carcinoma is frequently caused by dehiscent of oesophagogastric anastomosis. Change in principle was to initiate subtotal oesophagectomy as treatment of oesophageal carcinoma or other benign diseases, which require to removal of the oesophagus. 'Blunt dissection' is the main contribution. Reconstruction after this oesophagectomy requires the creation of a cervical anastomosis, which eventual dehiscence is not as fatal a complication as dehiscent of oesophagogastric or oesophagocolonic anastomosis situated in thoracic cavity. *Cervical anastomosis is possible manually or mechanically.* Advantages of instrumental anastmosis are generally known. *Problems are practical* application of available staplers in cervical area. The orifice of tunnel, which is formed *orthotopic or retrosternal, is relative narrow what limits manipulation with implantate,* tubulized stomach or thick intestine. Resection of sternoclavicular joint after successful oesophagectomy, which gives us better anatomical conditions for manipulation in the upper thoracal apertura, seems to traumatize excessively.

Effectivity of endoscopic oesophageal intubation in the palliation for advanced, oesophagus cancers

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Introduction: We evaluate the results of a series of 86 patients undergoing insertion of endoprosthesis (Rüsch) for palliation of inoperable oesophageal cancer.

Patient and methods: Between 1990 and 1997 we performed endoscopic intubation of the oesophagus in 86 cases because of inoperable oesophagus cancer. The patients had a mean age of 59·62 years, and the male to female ratio was 5:1. The tube insertion was managed under intravenous sedation. We used pulsion technique for the endoscopic intubation. The tumorous stenosis was dilated by Savary–Gilliard dilators. Most of the cases were not necessary X-ray control under the procedure. Thirty-six of 86 cases (41·8 per cent) we managed the intubation ambulatory. There was no mortality during hospitalization. After the intubation generally we precipitate minimal bleeding in 48 cases (55·8 per cent) but blood transfusion was not needed in any of the cases. In most cases retrosternal chest pain and 20 per cent of the cases subfebrility or fever appeared. In one case collar subcutaneous emphysema, pain, fever appeared, but contrast fluid 'outcome' was not identified by X-ray examination, surgical intervention was not necessary. Ten patients (11·6 per cent) have been admitted again with the occlusion of the tube, but endoscopic cleaning was succesful in all of them. We recognized tube migration in 9 cases (10·4 per cent). Most of the patients were able to have normal or semisolid food. The median survival was 18 weeks.

Conclusion: The endoscopic intubation of the esophagus is a safe, effective palliation for inoperable esophagus cancers. The method has numerous advantages as: might be ambulatory procedure, general anaesthesia not necessary, low morbidity, gives good quality of life.

Squamous cell carcinoma of the thoracic oesophagus following radiation therapy for breast cancer

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Radio-induced cancer is a rare pathology since only 30 cases of squamous cell carcinoma of the thoracic oesophagus following irradiation therapy for breast cancer have been reported to date. To be considered as a radio-induced cancer, these tumours must fulfil such criteria as a previous irradiation, the occurrence of cancer in the irradiated area, a sufficiently long period between irradiation therapy and the emergence of the tumour, the absence of other risk factors and a sex ratio different from usual ratio.

Between 1981 and 1995, among 3622 patients treated by mediastinal irradiation for breast cancer, we observed five cases of radiation-induced squamous cell carcinoma of the thoracic oesophagus. They were four women and one man (age 48–80) with no previous history of either smoking or alcohol abuse. The mean interval between irradiation and presentation with oesophageal cancer was 12·8 years (7–21). The tumour always appear in the irradiated area and was in all cases a squamous cell carcinoma. Treatment consisted of radiotherapy only, oesophagectomy, laser photocoagulation for a superficial tumour, and palliative treatment for two patients suffering from an advanced stage cancer with tracheal invasion, respectively.

These observations and the analysis of the literature indicate that: 1) radiotherapy treatment of the oesophageal cancer (exclusive or adjuvant) should take into account previous oesophageal radiation treatment; 2) the indications of curative excision surgery are the same as for other types of oesophageal cancers, but the anastomoses should be performed in a non-irradiated area; 3) excision by oesophageal stripping without thoracotomy is contraindicated because of the presence of peri-oesophageal sclerosis; 4) preventive measures in irradiation therapy for breast cancer are suggested.

Complications of endoscopic palliation of oesophagus cancer

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Aim: There is a great importance of the palliative treatment of oesophageal cancer because without different types of palliation the patients with inoperable oesophageal cancer have a poor quality of life. The predominant symptom is the various severity of swallowing inability that eventually progresses to complete dysphagia with hypersalivation, aspiration, rapid weight loss which eventually lead to death. The results of the surgical procedures of gastrostomy and jejunostomy are uncertain beause they are unable to prevent the complications caused by obstruction and aspiration. The aim of this study is to investigate the aspects of the procedure of palliative endoscopic oesophageal intubation that make possible to avoid gastrostomy and jejunostomy and to investigate the complications related this method.

Materials and methods: The palliative endoscopic intubation was entered in 1992 in our surgical department. Our procedure of endoscopical intubation is a simplified way of the method described by Tytgat in 1986. During the last five years 73 consecutive patients were treated with palliative fiberoscopic intubation with Tygon prothesis. Forty-six patients had esophageal carcinoma, 19 had tumours of the oesophago-gastric junction, 8 had pulmonary carcinoma obstructing the gullet. Among them 11 patients had broncho-oesophageal fistula. After the palliation the patients received High Dose Rate (HDR) after loading radiotherapy and telecobalt external treatment.

Resuls: After the endoscopical intubation the ability of swallowing improved in all of the cases and the bronchooesophageal fistulas were occluded. The complications were divided into three groups: early, late complications and other problems not related to the surgery. The early complications were perforations (7 patients), bleeding (1 patient). Two patients (2 per cent) died because of sepsis. The late complications were: food impaction (5 patients) tumour overgrowth (5 patients), tube migration in two cases when the tube moved proximally and was replaced by reintubation. We found the complaints of the reflux in all of the cardial tumorous cases. We found increase of body weight in 14 cases. Nineteen patients received intraluminal after loading radiotherapy.

Conclusions: The risk of perforation during endoscopical intubation is high, especially in the patients with tumours of distal oesophagus and the oesophago-gatric junction. On the base of previous data the rate of perforation after operative intubation is low, that is why the operative intubation is advised. The operative exploration is also a useful procedure because of the uncertainty of the CT and other examinations, and gives the possibility for the intraoperative staging and the checking of the position of the tube, as well. The improvement of quality of life is such an important result of the treatment as the improvement of the survival time due to better nutrition.

Long term results with pre-, postoperative and palliative LDR after-loading irradiation of oesophageal tumours

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Aim: Five years survival of oesophageal tumours is 7–10 per cent. To improve survival and quality of life, lumen restricting tumours were palliatively and preoperatively treated with LDR after-loading irradiation, 5FU chemotherapy, metallic stenting and enteric food preparations.

Materials and methods: Two hundred and nineteen patients, plus 72 patients preoperatively and 29 patients with recidive tumours were treated between 1982 and 1992. The dose delivered in 3 or 4 fractions was 50 Gy, protracted by 24 h, from a 5 mm distance to the mucosal layer. For setting up correct diagnosis and staging esophagoscopy, radiography, US and CT and iosotope examinations were carried out. Survival times and quality of life were assessed. The results were compared with the control group of 46 patients, who were refusing any treatment.

Results:

Survival	– preoperative	24 patients	39·6 months
	– recidive	15 patients	25·1 months
	– inoperable	219 patients	11·6 months
	– control	46 patients	8·2 months
Quality of life	– decreasing of dysphagia		69%
	– increasing of body weight		54%
	– diminishing of pain		74%

Conclusions: LDR Cs-137 after-loading method combined with chemotherapy and enteric food preparations proved to be efficient and significantly increases survival in preoperative and recidive cases of oesophageal tumours.

VIDEO PRESENTATIONS

Hernia and Abdominal Wall

The plug technique in umbilical hernia

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Aim of this study: The aim of this video is to demonstrate the surgical correction of an umbilical hernia with a prosthetic plug of mersilene mesh.

Materials and methods: We operated a female patient, 64 years old with umbilical hernia.

Steps of the procedure: 1) periumbilical incision and dissection of the hernia sac; 2) opening the sac and resection of incarcerated omentum; 3) excision of excessive sac tissue and closure of the opened sac; 4) set the plug in the umbilical orifice, to fill all the defect; 5) fixation of the plug, with the multiple stitches, to the umbilical borders; 6) closure of the wound.

Summary of results: The patient did well, was discharged of hospital in the next day to the operation and did not require analgesics at home. After a six month follow-up there was not recurrence of the hernia.

Conclusion: Plug technique, in umbilical hernia, is easy, safe and with no recurrence in our experience.

Infection

Protection by double gloving and reinforced gown: randomized evaluation using an electronic alarm contact detector

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Assessing the efficacy of the surgeon–patient barrier, a randomized controlled trial was designed with four crossed-over groups: simple or double gloves, and simple or reinforced gowns.

The Elper® device (Igea, Carpi, Italy) – a contact detector triggering an audible alarm – was used, controlled by a water leak test (American Standard for Testing Material). Glove perforations and glove or gown porosity were studied. 79 surgical procedures were monitored from January to April 1996 (238 surgeon-hours), by the same surgical team (151 person-procedures).

The highest alarms' rate were observed with wet gowns (32 alarms per 100 surgeon-hours), glove perforations (13 alarms per 100 surgeon-hours) and glove porosity (11 alarms per 100 surgeon-hours). The risk of glove perforation was higher in deep surgery (with visceral contact) than in superficial surgery (RR = 2·5; CI95 per cent: 1·2–5·3). The surgeons were unaware of 81 per cent of glove perforations. The rate of procedures with alarm(s) was lower with double compared to simple gloving (RR=0·6; CI95 per cent: 0·4–0·8), as for the rate of alarms per 100 surgeon-hours (RR=0·3, CI95 per cent: 0·2–0·4). Use of reinforced gowns showed no apparent benefit compared to simple gowns, whether for the rate of procedures with alarms (RR=1·2, CI95 per cent: 0·9–1·6), or for the rate of alarms per 100 surgeon-hours (RR=1·0; CI95 per cent: 0·8–1·4).

Double gloving should always be used. Contact detectors could help surgical barriers testing.

Possibilities of surgically solving the ischemic necroses of the skin and/or muscles of the forearm

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General approach: As a direct consequence of a trauma or of an incomplete and/or incorrect approach in emergency, the necroses may compromise the injured segment of the limb generating major morphological and functional problems. As for the surgical treatment applied, it varies from simple excision and covering (usually enough for skin necroses) to complex surgical procedures (the deep necroses, affecting muscles of the limb).

Material and methods: There are cases from two categories: a) wide skin necroses in which, due to the exposure of bone, vessels, nerve and tendons, it was necessary to use fasciocutaneous or musculocutaneous free flaps in order to cover the existing defects; b) necroses of the anterior compartment musculature, requesting flexors' reconstruction by musculocutaneous nerve supplied flaps.

A special case was that of a mangling trauma resulting in an association of crush and burn, causing both skin and muscles necroses; in order to solve this case we performed two simultaneous microsurgical free transfers: a fasciocutaneous flap and a nerve supplied musculocutaneous flap.

Results: We confronted good progress of all treated patients: a) complete good quality integration of the fasciocutaneous flaps; b) sufficient functional recovery for the musculocutaneous flaps, helping the patient to socially and professionally reintegrate.

Conclusions: 1) The correct first approach in emergency avoids problems such as ischemia. 2) Once these problems occurred there is only one solution of excision, fasciotomy and covering of the defects. 3) We consider that the best option for the skin-only defects would be the fasciocutaneous flaps and for the muscle defects requiring functional recovery the use of nerve supplied muscle flaps is needed.

Laparoscopic pericystectomy with the harmonic scalpel for hepatic hydatidosis: case report

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In this videoband, we present a case of hepatic hydatidosis treated by pericystectomy with the aid of the 'harmonic scalpel' apparatus (Ethicon).

The patient was a 47-year-old man with a computerized tomography revealed Gharbi grade III exophytic lesion (8 × 6 cm) at segment III. At the laparoscopic exploration, the cyst was found to be covered with omental adhesions which were divided with the aid of 'harmonic shears'. The cyst was removed by cutting in the plane between the cyst and hepatic paranchyma in the coagulation mode of the apparatus at full energy. Two hepatic ven branches (1–1·5 mm) and an arterial branch (1 mm) were observed as disting structures and secured with clips. At the end of the procedure, there was only minimal bleeding from the liver surface and this was controlled with the argon beam coagulator. Then the cyst was placed into a plastic bag and extracted after the cyst contents were partially removed. The postoperative course of the patient was uneventful. He was discharged after two days.

The harmonic scalpel greatly facilitates the procedure by sealing the 'raw' liver surface effectively, i.e. there was no leakage of bile and only minimal bleeding. With the aid of 'harmonic scalpel' or a similar apparatus, pericystectomy can be conveniently added to the armementarium of the laparoscopic surgeon. This operation should be performed in the institutions with extensive experience in both laparoscopic and hepatobiliary surgery.

Hydatid disease. Location, complications, diagnosis, and treatment. Social and economic importance

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Introduction: The hydatid disease is a zooanthroporosic parasitosis – a wide-spread ailment. It was first described in 1821 by M. Bremser. Liver is infected most often but the disease can also develop in other organs of the human body.

Methods: We discuss 87 cases with hydatid cysts located at different places in the body treated at our clinic during the period 1993–1997. We also discuss the study of approximately 15 per cent of the homeless dogs for bearing the parasite and the study of 100 random chosen vegetable samples from the green market for the eggs of the parasite.

Results and discussion: The operated patients are: 34 (39·08 per cent) males and 53 (60·92 per cent) females, aged from 15 to 80 years.

To diagnose the disease we used – clinic examination: 87 cases (100 per cent); rentgenography: 87 cases (100 per cent); angiography: 13 (14·94 per cent); CT: 34 (39·08 per cent); sonography: 87 (100 per cent); serological samples: 81 (93·10 per cent).

Complications before the operation were discovered in nine cases (10·34 per cent) – biliary peritonitis: 2 cases; broncho pleural fistula: 1 case; suppuration of the cyst: 2 cases; icterus: 1 case; cyst perforation: 3 cases.

80 (91·95 per cent) of the operated patients were completely cured. Seven (0·05%) of the cases developed new cysts of the liver after the first year of the operation.

The postoperative complications: infiltrations of the operative wounds infestation, suppurations, prolonged drainage. Fistulizations were discovered after the first month since the operation. Recurrences were discovered during the course of the first year after the operation.

79 (90·80 per cent) of the operated patients were traced. They did not show any consequences of the disease.

The average stay of the patients in the clinic is 15·4 days.

The average time for recovery and restart of work activities is 84·3 days. The average losses of working time for the enterprise is 100 working days.

In 45 per cent of the approximately 15 per cent of the examined homeless dogs the parasite was found.

Six per cent of the vegetable samples were also infected with the parasite eggs.

Conclusions: The applied methods of treatment of the solitary form of the hydatid disease are appropriate for its complete curing. The postoperative complications vanish during the first month after the operation. Recurrent cyst develop during the first year.

The problem – homeless dogs – hydatid disease – was placed on the agenda of the medical, veterinary and town authorities as one of vital social importance and significant consequences.

Left hepatectomy in cirrhotic liver using the harmonic scalpel

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Introduction: Bleeding is an important drawback during liver resection in patients with cirrhosis. The harmonic scalpel, an ultrasonically activated scalpel introduced by Amaral in 1993[1], could represent an improvement with respect to surgical cutting and coagulating during hepatic resection in this type of patient. We present a II-III segmentectomy for hepatocellular carcinoma in a cirrhotic patient using this recently introduced device.

Case report: A 72 year old man with a Child A liver cirrhosis, related to hepatitis C virus, with a 2 cm nodule in segment III, closed to right hepatic vein, has been operated on through a bilateral subcostal laparotomy. Intraoperative ultrasound did not find other nodules in the rest of liver parenchyma. Resection was performed with intermittent Pringle maneuver with complete occlusion during 15 minutes followed by 5 minutes of rest. Blood transfusion was not required. Ascites appeared during postoperative period was controlled with diuretic treatment.

[1] Amaral J.F., The experimental development of an ultrasonically activated scalpel for laparoscopic use. *Surg. Endosc. Laparoscopy* 4: 92–9, 1994.

Surgical treatment of achalasia by laparoscopy

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Introduction: In spite of the fact that pneumatic dilation of the cardia in achalasia offers some acceptable results, dysphagia, although diminished, usually reappears during the first months. We show a Heller myotomy associated with a Dor fundoplication in an achalasia patient, sent directly to surgery without previous dilation. The patient complained for year and half of progressive dysphagia and regurgitation, having lost 6 kg of weight. The X-ray study, endoscopy and manometry were compatible with achalasia, with tendency towards vigorous type and LESP at rest of 36 mmHg.

Material and methods: Five trocars of 10 mm were used, placed in right midclavicular line, left anterior axillary line, left middle clavicular line, subxyphoyd and upper middle line where the optics of 0° was placed. We carried out the complete dissection of the esophagic hiatus. Once dissected both crura, the esophagus was isolated creating a posterior window from right to left, surrounding it with a ribbon. At least about 7 cm of esophagus was freed identifying and peserving the anterior vagus. The myotomy was carried out with scissors without electrocoagulation and maintaining an intraesophageal bougie of 40F, beginning 2 cm below the gastroesophageal junction. We used the cardial artery like anatomical reference. The myotomy was prolonged upwards in about 6 cm being testing by intraoperative endoscopy its completion and the absence of perforation. We performed a partial fundoplication Dor type to avoid the gastroesophageal reflux.

Conclusion: The postoperative evolution was satisfactory. After one year the patient is totally asymptomatic without dysphagia, nor pyrosis. The manometry show a high pressure zone of 3 cm of length with 8 mmHg and a pHmetry without pathologic reflux.

Subtotal left hepatic lobectomy

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The principle of hepatic resections is founded on the plurisegmental anatomy of the liver. According to Couinaud's classification, left hepatic lobectomy corresponds to the removal of the II and III segments. In order to perform a guided resection, it is necessary to divide the left supra-hepatic vein in correspondence of its outflow into the caval vein or into the middle supra-hepatic vein. Obviously, it is also necessary to interrupt the biliary, portal and arterial branches of the hepatic pedicle in connection to such segments. The crucial point of the operation is undoubtedly represented by the identification and ligature of the left supra-hepatic vein on the right site of its outflow. In fact, it may drain directly into the caval vein, as well as into the middle supra-hepatic vein. Since a correct intraparenchymal identification of the left supra-hepatic vein is considered mandatory, in order to avoid complications, such as dangerous hemorrhages, due to caval lesions, or accidental ligature of the middle-supra-hepatic vein. In some cases, where a total left lobectomy is not considered essential to the aims of the operation, it may be performed a left subtotal lobectomy, in which the ventral branch of division of the left-supra-hepatic vein is preserved and used as a guide to identify the dorsal branch, which may be easily divided. By the way, any complication of severe hemorrhage or accidental ligature of the middle supra-hepatic vein is highly reduced. The authors show the fundamental stages of the intervention of subtotal left hepatic lobectomy, performed in a female 53 year old patient, due to the presence of a large suppurated cyst of the left hepatic lobe in association to a pseudo-inflammatory hepatic tumour.

Traumatic rupture of the trachea and esophagus solved by primary suture

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Authors present an unusual case of complete traumatic rupture of the neck part of trachea with almost complete rupture of esophagus. In spite of more than 48 hours time delay since injury, they decided to perform a primary reconstruction of trachea and esophagus. They describe an original way of reconstruction of trachea with a T-type silicone tube in a presence of dilaceration of trachea and fracture of the arch of cricoid cartilage. In spite of a complete rupture of trachea with dilaceration and with distraction of parts of trachea they achieved a perfect reconstruction with the vocal function remaining.

Video-assisted thoracoscopic lung biopsy – the new diagnostic procedure in case of disseminated pulmonary diseases

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Sometimes patients have more than one organ or system affected by infections or neoplasia or other diseases, requiring quick and precise diagnostic investigation. In these situations, different invasive diagnostic procedures may be necessary. Open, or nowadays video-assisted lung biopsy is required to clarify the pulmonary diagnosis. The new method has been used in our department from May of 1994. We have performed 35 VA(S-k)assen biopsy (male: 18, female: 17). Mean age 48·3 (26–67) years. In two cases we had to make a conversion. There were no severe complications and mortality. Most patients had pulmonary fibrosis and sarcoidosis. We conclude, that video-assisted thoracoscopic technique of lung biopsy is simple, useful, and safe.

Wide-en-bloc resection of giant right adrenal tumour

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Interventions of wide-en-bloc resections of adrenal tumours involving adjacent organs have been reported. They may include nephrectomy, splenectomy, hepatic, pancreatic, intestinal resections according to the extension of the tumour and the degree of infiltration of the peritumoral organs. The authors report the case of a 63-year old female patient undergone wide-en-bloc resection of a giant right adrenal tumour, including right nephrectomy. CT scan showed the presence of a retroperitoneal mass, 13×18 cm, extending itself from the diaphragm, with compression of the right lobe of the liver, down to the posterior wall of the right kidney, which appeared dislocated in an anterior plane together with the caval vein. The principal stages of the operation were: 1) Right thoracophrenolaparotomy. 2) Adequate mobilization of the liver by incision of its round, suspensor, triangular and coronary ligaments. 3) Preparation of the suprahepatic caval vein in order to clamp it in case of necessity. 4) Preparation of the retro-hepatic and subhepatic caval vein with isolation of both renal veins. 5) Isolation of the right ureter. 6) Mobilization of the tumoral mass, deeply located in the retroperitonal space, by freeing it from the posterior plane. 7) Wide-en-bloc resection of the tumour including right nephrectomy. The authors stress the necessity of accurate preparation of the caval vein before any attempt to remove the adrenal tumour, because of possible dangerous intraoperative hemorrhage, due to accidental laceration of adrenal veins.

Near total thyroidectomy

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Surgical removal of the thyroid gland may be complete, as in total thyroidectomy, or incomplete. In the last case, it may be a subtotal thyroidectomy, where it is presumed that the residual tissue may be sufficient to maintain the hormonal function, and a 'near total' thyroidectomy, where the remaining tissue is so minimal not be be sufficient to guarantee any functional activity. Thereby, the 'near total' thyroidectomy is functionally compared to a total thyroidectomy. The choice of this procedure is strictly connected to technical reasons, in order to avoid the possible complications commonly reported in a total thyroidectomy. These are represented by an increased rate of damage to the parathyroid glands, with the effect of a permanent postoperative hypoparathyroidism, as well as by lesions to the recurrent nerves. The authors describe the technique used in performing a 'near total thyroidectomy', with particular regard to the principal stages of the intervention that may favour the preservation of the parathyroid glands as well as of the recurrent nerves. These principally consist in: 1) a preservation of a small pretracheal fibrotic lamina in correspondence of the superior pole of the thyroid, where the recurrent nerve strictly adheres to the thyroid capsule. 2) a lower ligature of the superior thyroid artery comprising a minimal quantity of glandular parenchyma. The reason for it is that of offering a better vascularization of the superior parathyroid glands, by preserving the posterior thyroid vessels, as well as that of avoiding their accidental removal.

The percutaneous treatment of the thyroid gland's cysts

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Purpose: To evaluate the efficiency of the percutaneous treatment of the thyroid glands cysts of various causes under the sonographic control.
Materials and methods: Since 1991 to 1996 the percutaneous treatment of the thyroid gland's cysts was used in 293 patients. The majority of them (90 per cent) were women. The localization of the cysts was, as a rule, in right or left lobes in equal frequency, rather seldom – in the isthmus. The diameter of cysts was from 5 mm to 80 mm. The selection of a secure approach to the cysts was carried out under the sonographic control. We used 7·5 MHz-transducer. The color Doppler device was used in order to avoid both the gland and vessel damage. A fine-needle puncture of the thyroid gland was performed with aspiration of the content of a cyst after detecting the secure approach. The etiology of cysts was, as a rule (67 per cent), the hemorrhage in the thyroid parenchyma or the destruction of adenoma-like node, which had been confirmed by cytologic investigation of the aspirated material. The frequency of so-called 'virtual' cysts was 25 per cent. The features of virtuality are: distinct capsulae, the transparent content and the typical elements of a cyst's internal cover. In such cases sclerotherapy by injection of the 96 per cent ethyl-alcohol was carried out after the aspiration. The amount of alcohol to be injected was 60 per cent of the cyst's volume. The cytologic investigation revealed malignant cysts in 6 per cent of all cases.
Results: Good further results are obtained in 60 per cent of cases: the absence of residual cyst 12 months after the percutaneous aspiration. In cases of a sclerotherapy no residual cyst was revealed in 12 months after the treatment. 20 per cent of the patients with residual cysts have undergone additional percutaneous aspirations with good results. The remaining 20 per cent of the patients were operated because additional aspirations had been resultless.
Conclusion: The percutaneous aspiration of the cysts of the thyroid gland under the sonographic control is minimally-traumatic, efficient and profitable method of the treatment.

Laser photocoagulation of thyroid neoplasms

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Purpose: To study the efficiency of ND-YAG laser treatment, in the regime of the interstitial therapy, of both thyroid nodes and residual cysts after the aspiration. To find out an optimal possible regime of the photocoagulation using the light-conductor which has the sideradiation, and using the ITT-light-conductor.
Materials and methods: The photocoagulation was performed after percutaneous puncture of the thyroid neoplasm. The ND-YAG-Fibertom laser, the empty-light-conductors and the ITT-light conductors were used. The light-conductor was led to the zone of interest through the lumen of a punction needle under sonographic control. Three seances of photocoagulation of nodes, 10–15 mm diameter, were performed, as well as two seances with nude fiber, power 10 wt and 3 sec-exposure. One seance of ITT-light-conductor therapy, power 5 wt with exposure 20 sec was performed. The laser photocoagulation of the walls of cysts was performed after the aspiration of its contents in four patients. The diameter of cysts was from 20 to 40 mm. The nude light-conductor was used, the radiation power was 10 wt, the exposure was 6 sec. The hyper-echo zone, connected with gas artifacts and obstacling the correct visualization, was detected in all cases of the sonographic control.
Results: No one complication was revealed. The hyper-echo zones in the points of laser treatment were detected one year after the photocoagulation. Both cysts and nodes recidives, as well as far-time complications after therapy were not revealed.
Conclusion: So, the interstitial laser thermotherapy is both efficient and efficient and safe method of the treatment of thyroid diseases, accompanied with the cysts and nodes. Further elaborating and amendment of this prospect method will allow to broaden the area of its use.

Laparoscopic versus mini-laparotomy approach for lumbar sympathectomy

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A total of 20 patients with severe lower leg ischaemia (Fontaine III. st.) caused by popliteocrural arterial occlusion underwent lumbar sympathectomy in general anaesthesia. It was the aim of this study to develop a minimal invasive approach for this procedure, with less invasivity and shorter operating time than the traditional translumbar gridiron incision. Patients have been randomly selected in two groups. In group I (10 patients) we applied laparoscopic retroperitoneal approach, with insufflation using three ports, and normal laparoscopic instrumentarium. In group II (10 patients), we performed a 3 cm long minilaparotomy incision with gridiron lumbar transmuscular approach using the 'Rozsos' device, a specially developed lighting retractor system. We considered the procedure a successful one if the intervention could be performed within half an hour and without any intraoperative complication. The operation was converted for the traditional open gridiron incision when it could not be accomplished within 30 minutes. Group I: except one all laparoscopic attempts have to be converted success rate 1/9, three minor complications occurred. Group II: all the 10 procedures have been completed within 8–14 minutes, only one complication occurred, and the hospitalization was 2–4 postoperative days. Following this randomized clinical study, we performed further 27 lumbar sympathectomies from minimal invasive direct access using the 'Rozsos' retractors, with the same satisfactory result.

It is our conclusion that the mini-laparotomy approach for lumbar sympathectomy with 'Rozsos' retractor system is superior to the traditional translumbar open, or laparoscopic approach in regard to operation time, invasivity, complication rate and recovery.

Reconstruction of a bilateral congenital renal artery stenosis

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This video presentation shows a surgical procedure in case of a bilateral congenital renal artery stenosis. This 16-year old girl had severe hypertension since her early childhood which worsened since she became adolescent. The maximum value of blood pressure was 190 over 140 mm of mercury. She required combined medication of four anti-hypertensive drugs. No sign of renal insufficiency could be obtained. DSA renal angiography revealed high grade bilateral renal artery stenosis with post-stenotic dilatation at the orifices typical for congenital origin. There was no evidence of any specific inflammatory disease like Takayasu's arteritis.

During surgery the renal arteries were approached through a midline incision. The retroperitoneal space was entered paraduodenally and the renal arteries were prepared for clamping. Patient was anticoagulated and both renal arteries were ligated. Transection of the dilated parts was followed by direct reimplantation into the aorta with continuous suture. The entire clamping time was 24 minutes. After having released circulation diuresis started. Anticoagulation was reversed and the wound was closed over suction drain. The postoperative course was uneventful. Blood pressure returned to normal. The patient was discharged at the 7th postoperative day and required salicylate medication only.

Conclusion: Congenital renal artery stenosis – those are not suitable for dilatation – can be treated by surgery. Direct replantation can be done with low ischemic risk and provides good results at long run.

The use of the fasciocutaneous forearm free flap as a cutaneous and vascular graft

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General approach: In certain casualties, the amputation (either complete or partial) occurs associated to large soft tissue losses. In such casualties, for treating the tissue losses, we very much shorten the bone segments – sometimes even an entire segment of the limb. One of the alternatives for such casualties is the free microsurgical transfer of a fasciocutaneous flap having its skin elements used for covering the soft tissue losses and its vessel pedicle used as a vessel graft for the blood supply of the amputated limb.

Material and method: There are here presented some casualties with partial or complete amputation of the forearm and of the calf.

In both situations – with large soft tissue losses — we used a fasciocutaneous radial forearm free flap using its skin component for covering the defects and its vessel pedicle as a vessel graft in order to re-achieve the blood supply of the area.

Results: The flaps had a perfect integration resulting in a good covering as well as good viability of the amputated segments.

Therefore, in order to avoid the excessive shortening of amputated limb segments, the use of fasciocutaneous free flaps with double role appears as an important method of treatment.

Haemorroidectomy – Ferguson Technique with diathermic dissection

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Aim of the study: The aim of this video is to demonstrate the technique of Ferguson haemorrhoidectomy with diathermic dissection
Materials and methods: Use of a disposable enema two hours before the operation Patient in prone jackknife position Posterior perineal block with bupivacaine for control of postoperative pain Rectal exam and definition of the piles and skin bridges. Entire dissection of the piles with diathermy indentifying and sparing the internal anal sphincter Ligation of the narrow pedicle of the dissected pile with 2/0 cromic and closure of the mucosa and anoderm, without tension, with a running suture.
Summary of results: We didn't find intense postoperative pain, and bleeding, sepsis or anal stenosis
Conclusions: The Ferguson technique with diathermic dissection showed to be a safe procedure with good results with less bleeding than the classic techniques

Endoscopic transrectal resection of rectalvillous tumours using an urologic resectoscope

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Introduction: The use of a 'rectum resector' similar to a cystoscope was reported in treatment of villous tumours of the rectum.
Technique: The patient is placed in the dorsal lithotomy position; the standard urologic resectoscope is then inserted into the rectum using the obturator. After the instrument is placed under vision through the lesion, the resection is begun in much the same manner as a transuretheral resection of the prostate. The tumour is resected flat to the adjacent normal rectal wall. Resection is carried out circumferentially around the lumen until all tumour is removed. The irrigant carries the chips and blood into the colon and allows excellent visualization without anal dilatation. A few chips are gathered for pathologic examination.
Patients and results: This technique has been performed in 20 patients, with a mean age of 74 years, presenting a rectal villous tumour. No mortality or morbidity were observed. The average operative time was 35 minutes and the average hospital stay was four days. There was only one recurrence treated by laser at follow-up ranging 14 to 48 months.
Conclusion: This endoscopic procedure is safe, nonexpensive, easily available and does not require anaesthesia; it seems to offer adequate surgery in rectal villous tumours.

Colo-dentate line anastomosis for low rectal cancer

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The aim of the video is to describe the particularities of a low anterior rectal resection for a cancer situated at 4 cm from the anal verge, considering both the oncological and the functional aspects. Several technical comments are proposed:

- The lower tumour level must be at least 4 cm from the anal verge, in order to have the usual 2 cm free margin below; if not, the anal canal under the dentate line would be resected and the anal continence would be compromized.
- A total mesorectum resection is performed, the dissection being done in the avascular space. All the lymph nodes from the inferior mesenteric artery territory are resected: for this reason, this technique is probably better than a local excision, taking into account the risk of early lymph node invasion of a small rectal cancer. This technique has also the advantage to widely excavate the pelvic cavity and thus facilitate the low mobilization of the rectum, particularly for a narrow pelvis in a man.
- Only supposed low Dukes' A cancers are eligible for this kind of conservative resection, the half upper part of the internal sphincter being resected just upper the dentate line. If the tumour invades the perirectal tissues (Dukes B) at this level, it would be necessary to resect a part of the pelvic floor to obtain a lateral free margin: thus, a Miles' procedure would be necessary.
- In this technique, the colo-dentate line anastomosis cannot be performed with a stapler: it would destroy the remaining lower part of the anal canal under the dentate line. The anastomosis is routinely performed through the anal canal using a hand suture. A diverting loop colostomy is performed to prevent the risk of fistulae.
- Six patients were operated using this technique between February 1994 and June 1997. All were Dukes' A except one with early lymph nodes invasion in the mesorectum. No patient had preoperative pelvic irradiation except one. During the first postoperative months, the functional results were poor: incontinence, multiple daily bowel movements. However, the results improved spontaneously during the first year. At this time, no patient presents sign of recurrence.

In conclusion, the colo-dentate line anastomosis seems a good alternative to a local excision or a Miles' procedure for a low rectal cancer, supposed it will be a Dukes' A tumour: it allows a low resection while the usual carcinologic rules are respected.

Abdomino-transsphincteric resection of the rectum for distal rectal cancer

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Sphincter-saving resection for cancer of the distal third of the rectum is performed in increasing percentage of the cases. From 01.01.1994 to 31.12.1996, 43 patients were operated on for cancer of the distal third of the rectum. The rate of sphincter-saving resections was 62·8 per cent (27 cases). In 13 cases the abdomino-transsphincteric resection, as described by Lazorthes, was used.

The aim of this video is to present this technique.

The patient is placed in the right lateral position, with the left leg elevated to permit the simultaneous exposure of the abdomen and perineum. The laparotomy is made by a curved incision in the left inferior quadrant. After high ligation of the inferior mesenteric vessels and full mobilization of the splenic flexure, the dissection is carried down as low as possible in the pelvis.

A second incision from the sacrum to the anus is made, de coccyx is excised, the levator muscles and the external sphincters are divided in the midline. The dissection of the distal rectum and anal canal is completed. The previously divided sigmoid colon is pulled in the perineal wound and the resection is performed leaving a safe distance below the tumour. The whole mesorectum is excised. The anastomosis is performed either by hand suture or double stapling technique. The sphincter and levator muscles are then reconstructed. A diverting colostomy is applied for 6 to 8 weeks.

The abdomino-transsphincteric resection is an excellent possibility to further improve the rate of sphincter preservation in cancers of the distal third of the rectum. It is especially useful in cases with narrow pelvis or bulky tumour, in which an anterior resection is not always possible.

A new method of creation of an artificial anal sphincter with use of pedunculated muscle of the small intestine

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The authors present their own method for the formation of a pseudosphincter for a faecal fistula. The pseudosphincter is formed of a pedunculated seromuscular flap of the small intestine. The method of pseudosphincter formation was used in 30 patients undergoing the abdominoperineal amputation of the rectum. The patients presented with advanced stages of rectal cancer (B and C according to the Dukes Scale). Abdominal stoma with a pseudosphincter was formed in 17 patients; in the remaining 13 patients the pseudosphincter was formed in the perineum. There was no perioperative mortality. Ultrasound scan, manometry and clinical assessment proved appropriate functioning of pseudosphincters. We believe that pseudosphincter formation with a pedunculated seromuscular flap of the small intestine can be recommended as an alternative means of preventing uncontrolled stool loss through a faecal fistula.

Staplers in colorectal oncosurgery. Modified operative technique

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For a five year period (1993–1997) 406 operations for colorectal cancer have been done in the Department of General Surgery, 103 of which ned by 'Autosuture' staplers. From the total of 55 cases of anterior resections, 36 were low anterior resections – down to 3 cm from the anal verge.

The advantages of stapler colorectal oncosurgery techniques are outlined: safety, lesser risk of postoperative suppurative complications, time saving and greater possibility for low anterior rectal resections.

The authors describe and demonstrate on video original modification of established operative technique for colonic anastomosis, using only two GIA staplers.

Creation of the arterio-venous fistula for hemodialysis using transposed basilic vein on the arm

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The film demonstrates technical details of a-v fistula creation.

In the cases of irreparable failure or impossibility of performing AVF on the forearm, profitable alternative is the basilic vein on the arm.We find it through incision just below the elbow. After cutting it at this level, we ligate distal end and prepare vein from surrounding tissue. Collaterals are meticulously ligated. The incision is prolonged to the axilla. Next we rinse vein with the heparinized saline, enlarging it this way. The wound is sutured. Through another incision at the elbow level we prepare the brachial artery. Using special curved device (tuneller) we place basilic vein subcutaneously on antero-lateral surface of the arm. The vein is anastomosed with the artery end to side with vascular sutures 6–0. Thrill confirms good work of fistula. Suturing of the wounds ends operation.

Autogenous vein is an excellent material for AVF. The risk of infection is very low. Only one anastomosis is needed. The fistula is easy to inject and the blood flow is over 300 ml/min. We performed 45 fistulas that way and the patency rate is 80 per cent and 70 per cent after one and two years, respectively.

Creation of the A-V fistula for hemodialysis using PTFE graft on the arm

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The film demonstrates technical details of arterio-venous fistula (AVF) creation.

In cases where autogenous material is completely exhausted or unsuitable for AVF we use PTFE tapered prosthesis. First incision is made in axilla to expose axillary vein. Collaterals are ligated. The second incision is performed on elbow level. Here we prepare the brachial artery. Both artery and vein are clamped. Using special curved device (tuneller) we make subcutaneous tunnel on antero-lateral surface of the arm. Prosthesis is placed in the tunnel. Two vascular anastomosis are made (end to side) between prosthesis, artery and vein. Arterial anastomosis is 4–5 mm and venous 6–8 mm length. Clamps are removed and the fistula is ready. Thrill confirms proper work. Skin suturing ends operation.

PTFE prosthesis is very good solution for patients with poor veins. Blood flow is over 300 ml/min. It is easy to perform and puncture. If it is made aseptically, the risk of infection is relatively low. Patency rate in 30 cases is 70 per cent and 60 per cent after one and two years, respectively.

Facial palsy – long term experience with modified McLaughlin's and Gillies technique

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The patterns of facial palsy vary in the degree of involvement and duration. A complete assessment of the neural and muscular status is necessary in patients presenting with partial, segmental, or complete paralysis. No single surgical technique can accomplish the most important goals of rehabilitation of the complete paralysis, which should be a normal appearance at rest and symmetry with voluntary and involuntary motion. When direct nerve suture, autogenous nerve grafting, and nerve crossover are inapplicable in the rehabilitation of the paralyzed face, dynamic support using the temporal muscle is a proven reconstructive technique. This method enables complete lid closure and active movement of the lips and cheeks, therefore improving speech.

Since 1972, we have performed a modification of McLaughlin's technique attaching a fascialata strip through the separated coronoid process and suturing this to the nasolabial fold and the orbicularis oris muscle in the midlines of the upper and lower lips. At the same time restoration of lagophthalmus is done by transposition of a temporal muscle segment, enlarged by his own fascia as described by Gillies.

The most important factor of this procedure is the obtaining of satisfactory movements by overcorrection and immediate postoperative training. Advantages of this method are an excellent appearance at rest and good symmetry with voluntary motion, ocular sphincter control and no loss of other significant functions. This one step procedure achieves an immediate facial rehabilitation.

The results of our series of 132 patients with a median follow up of 9·7 years demonstrate the possibilities of this technique. The average degree of reanimation in the nasolabial fold is 6·8 mm (range 4–16 mm). A complete lid closure was obtained in 87 per cent. The rewarding improvements in the psychological sequels emphasize the value of this method especially in chronic cases of complete facial paralysis in the elderly patient.

Unusual form and localization of the hydatid disease

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Primary retroperitoneal hydatid cyst without involvement of another peritoneal organ is extremely rare, especially alveolar form of the hydatid disease.

Case report: A 62-year old woman with a six month history of pain in right hypochondrium and right lumbar fossa was referred to us. Ultrasonographic examination of the abdomen revealed a cystic lesion lying in the right hypochondrium, near the right kidney – suspected hydatid cyst. Laboratory findings and chest X-ray examination were normal. Immunological test, complement fixation was positive.

At exploratory laparotomy abdominal contents were normal. After incision of the posterior peritoneum we found a large cyst with multivesicular infiltrative structures – alveolar form of the hydatid disease.

The treatment of the cyst was by evacuation of the cyst contents and reduction of the cyst. We used hypertonic saline and finally we drained this space with two drains. Postoperative period was normal. Albendazole adjuvant chemotherapy was given to the patient three months.

Comment: Echinococcus multilocularis cause alveolar hydatid disease. The probable mode of spread of the hydatid embrio to the retroperitoneal space is either via the lymphatic from the gastrointestinal tract or via the portal system of the liver.

In the period of the last 15 years in our department were operated 98 cases with hydatid disease, and all of them were cystic form of the hydatid disease. This case was only retroperitoneal one in the series. The hydatid disease a fairly common disease can become very difficult and even impossible to diagnose. The most important factor in diagnosing hydatid disease is the awareness of its possibility.

Different localizations of the hydatid disease

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Introduction: Hydatid disease remains a big problem for the patient and surgeon especially when it affects multiple sites, which need different surgical treatment. The authors present a rare case of the patient with four distinct sites of echinococcus cysts which were treated in the period of two years.

Materials and methods: A 56-year-old woman admitted to the hospital with right hypochondrial pain and palpable mass. Ultrasonography at the abdomen show the large echinococcus cyst with daughter cysts into the right lobe at the liver and a echinococcus cyst at the right ovary. Both cysts were treated at same time. After 18 months at the routine follow-up we found big echinococcus cyst at the spleen and another cyst in the pelvic cavity – secondary echinococcis.

Results: In this video presentation different methods of management of hydatid disease were presented in the same patient. Evacuation of the cyst contents, partial pericystectomy, scolicid treatment of the cyst, visualization and closure of communicating bile ducts, omentoplasty and drainage, were the method of choice at the treatment of liver hydatidosis. Primary hydatid cyst of the ovaries is very rare. The disease is usually acquired in childhood and may take from five to 20 years before it is diagnosed. The surgical treatment was removing the ovary, fallopian tubes and cyst. Echinococcus of the spleen is also very rare. In our case there was a large cyst with destruction of the spleen tissue and the only one management in this case was splenectomy. The secondary echinococcosis is possible, especially if we have had bad isolation and scolicid treatment. The treatment of the pelvic cyst was evacuation, pericystectomy and drainage.

Conclusion: The surgical treatment of the hydatid disease can be different. It depends on cyst localization and organ destruction.

Gasless operative laparoscopy: five years of experience

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Pneumoperitoneum is a limiting factor for Operative Laparoscopy. Rare but dramatic are the accidents linked to the 'blind' realisation. Contraindications are patients with cardiopumonary risk, politrauma with suspected or clear hemoperitoneum (hazard of gas embolism); epidural anaesthesia is also a contraindication. For these reasons, in our department, in 1993 we have started the Gasless Operative Laparoscopy Project (GOLP). The possibility to obtain an effective working chamber by mechanical elevation of the cutaneous plane brought us to carry out a mechanical arm with two steel needles an 'open celioscopy'. With this procedure we obtain a working chamber similar to the pneumoperitoneum. This device (Laparotenser), permits to use unvalved ports, to perform a minilaparotomy for operative purpose without compromission of the working chamber. This technique demonstrate to be effective, safe and economic. This method has therefore been shown to provide the following advantages: no changes in the hemodynamic and blood gas parameters; no postoperative shoulder pain; permits epidural anaesthesia; permits continuous suction without compromising the work chamber; eliminates the need for valved ports; reduces overall costs.

Our experience is the following: cholecystectomy 464; colonic resection 32; diagnostic laparoscopy 22; adhesiolysis 15; hernyorraphy 9; appendicectomy 8; duodenorraphy 4; ilel resection 3; gastroenteroanastomosis 3; foreign body ablatio 3; hepatic fracture 3; hepatic cyst fenestration 3; spermatic vein ligation 2. Total: 570.

Pancreaticojejunostomy on a separate loop after duodenopancreatectomy

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The pathological entities known as periampullar malignancies (duodenal malignancies, pancreatic adenocarcinoma, malignancies of the distal common bile duct, malignancies of the hepatopancreatic ampulla) represent an increasing number of dreaded diseases and became well known and quite common. They require surgical treatment: rarely intervention, often palliative procedures.

We performed in our clinic a study of 60 cases of periampular malignancies in which the standard surgical treatment was pancreaticoduodenectomy, as a radical surgical intervention. It represents the experience of our clinic in the last 30 years.

We studied the reconstructive procedures, in order to achieve a safe technique that allows the decrease of the postoperative morbidity and mortality rates. The high postoperative morbidity rate of the 'classical' reconstructive procedures is due to fistulas of the pancreaticojejunostomies – pancreatic fistulas which can become complex bilio-pancreatico alimentary fistulas.

We obtained best results using pancreaticojejunostomy on a separate jejunal loop, dissociated from the biliojejunostomy and gastrojejunostomy. We obtained a safe biliary and digestive continuous transit, and a derived pancreaticojejunal transit. In the 60 dudodenopancreatectomy done this type of reconstruction was realized in 42 cases, with a decreased morbidity and mortality rate compared to the classical methods.

Jurasz operation performed by laparoscopy

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Aim: The authors present a cystogastrostomy (Jurasz procedure) performed by laparoscopy.

Material and methods: The operation is performed for a pseudocyst of 6 cm of diameter persisting five months after acute pancreatitis. As demonstrated by CT scanner, the cyst is displacing anteriorly the medium part of the stomach.

The operation starts with a conventional laparoscopy. Afterwards, three trocars (one of 10 mm for the laparoscope and two of 5 mm for the various instruments) are introduced directly in the lumen of the stomach to perform the cystogastromy.

To facilitate the further introduction of the trocars in the stomach cavity, the anterior wall of the organ is anchored at the abdominal wall. The stomach is insufflated via the port of a 10 mm blunt trocar whose special design will prevent any gas leakage. The laparoscope is introduced into that trocar, a good visualization of the inside of the stomach is then obtained and the Jurasz procedure is performed. A cystography is first realised to determine the inferior part of the cyst. The cystogastrostomy is done at that level. At the end of the procedure, a nasogastric tube is left in place.

Conclusion: The postoperative evolution is uneventful. The patient is discharged from the clinic on the third day. A CT scan is performed one month postoperatively; the pseudocyst has completely disappeared.

Extended lymph node dissection during whipple procedure

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Aim of the study: The results of pancreatoduodenectomy for the carcinoma of the pancreatic head have been disappointing. The five-year survival rate is about 10–15 per cent. Probably the insufficient lymph node clearance might be the cause of the local recurrence. For this reason some authors offer the extended lymph node dissection during Whipple procedure in order to improve the survival rate. The present video shows our first experience with this operation.

Materials and methods: We prefer the pylorus-preserving pancreatoduodenectomy, if there is no oncological contraindication of that. However this procedure was completed with regional and juxta-regional lymph node and connective tissue clearance.

Summary of results: Although the operation was longer because of the dissection, it did not result in further complication.

Conclusions: Our early experience is advantageous with this extended procedure. Although its positive effect could not be measured yet, the improvement of the survival time will be expected.

Laparoscopic pancreatic cystogastrostomy. A simplified technique

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Patient: A 69-year old caucasian female patient, admitted for electivel surgical treatment of a symptomatic pancreatic pseudocyst.

History: A conventional cholecystectomy had been performed eight years before. An ERCP with endoscopic papillotomy was made three months earlier to treat an acute pancreatitis with persistent papillary obstruction by an impacted gallstone. Ultrasound and preoperative CT scan showed a pancreatic pseudocyst (12 cm diameter) in close contact with the posterior gastric wall. Fluid content was predominant.

Procedure: Under general anaesthesia, a transumbilical videolaparoscopy was started. Three other trocars were introduced into the peritoneal cavity in a standard position to gastric surgery.

1) Anterior gastric wall was opened. 2) Cyst puncture. 3) Cyst opening by a 2 cm window. 4) A multifire Endo-GIA 30 was introduced. 5) A stappler side-to-side pancreatic cystogastrostomy was performed. 6) The cyst cavity was cleaned. 7) Anterior gastric wall was closed by a 2/0 PDS continuous suture. 8) The procedure was finished.

Postoperative control: No complications were detected.

Training for advanced laparoscopic biliary procedures using a pig model

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Although perioperative endoscopic retrograde cholangiopancreatography may be a preferred method for handling common bile duct stones in the laparoscopic era, laparoscopic common bile duct (CBD) exploration is also being promoted. Surgeons who have gained experience and confidence with laparoscopic cholecystectomy are now applying the minimally invasive approach to other biliary procedures such as common bile duct stones and obstructive jaundice.

Our eight minute video demonstration shows a prepared pig model, by which one can acquire experience for the technique of laparoscopic CBD exploration. The small size of the cystic duct and common bile duct in the pig makes it difficult for most to learn and practice laparoscopic common bile duct surgery. For this reason authors prepared a pig model by performing a common bile duct ligation 5–6 days prior to the planned training. The anatomy of the pig's biliary system is similar to the human, except for two things. The pancreatic duct does not enter the duodenum through the common bile duct ampulla, which means that the ligation of the distal common bile duct does not interfere with the pancreas. The other dissimilarity is that in pigs the cystic duct frequently arises from the right hepatic duct, which can make choledochoscopy more challenging. The ligation of CBD was also performed laparoscopically using clips. After as few as six days the CBD became dilated by 2 and 2·5 cm, and this was well tolerated by the animal. The training of advanced laparoscopic biliary procedures were thus possible as presented on the videotape, such as choledochoscopy, exploration of the bile duct, T-tube placement and it's fixation with intracorporeal suturing and knotting.

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Transplantation

Technique for free intestinal loop for urethral reconstruction

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The urethral reconstruction is a very complex problem and the usual techniques are often associated to a severe morbidity.

This video shows the appliance of a free intestinal graft for extensive urethroplasty. This method was studied in our Department and applied in man after several studies in the experimentation animal.

Two patients underwent perineal urethrostomy: one with partial loss of penis and urethral avulsion for trauma and the other with pseudo hermaphroditism.

All steps of this technique are visualized: receiver vessels building through saphenous vein grafts; intestinal loop gathering and transposition; 'neo urethra" diameter molding; follow-up.

After a period of 10 and four years respectively, the patients void well and uniformly. No complications have occurred.

Laparoscopic biliopancreatic bypass, experimental model

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Objective: In 150 vertical gastroplasties performed by our group for the treatment of morbid obesity with more than 10 years follow-up, the outcomes has not been as good as expected, with poor body mass loss and even refattening. Thus, we began to apply the biliopancreatic bypass which combines both restrictive and malabsorption techniques with a clinical experience of 30 patients in the last three years with good results and no complications. In this videotape we show an experimental variant of this technique outlined to be performed by laparoscopic approach in pigs, in order to further application in human surgery.
Method: The technique was carried out in 10 Landrace pigs. The follow up was seven days only because the aim of the study was to demonstrate the feasibility of the laparoscopic technique without complications.
Results: The biliopancreatic bypass was performed in all the animals with a mean operating time of 3·2 hours and without any intra or postoperative complication.
Technical description: After total anesthesia with orotracheal intubation, the animal is settled upwards and 20° antitrendelemburg. Once a pneumoperitoneum of 12 mmHg is created, five 12 mm ports are inserted. The liver is retracted right and upwards and the posterior space of the stomach is opened through the great omentum. An horizontal gastric stapling is performed, creating a proximal gastric pouch of 50 ml. Counting 250 cms. afterwards from the ileocecal valve, the jejunum is divided and an Y Roux loop is performed with first a gastrojejunal anastomosis and a jejunoileal anastomosis at 50 cms from the ileocecal junction. All this sutures were done by both endostapler and endostitches techniques.

An eventual iatrogenic choledocal lesion during a laparoscopic cholecystectomy. Main points to consider in order to avoid this complication

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Aim of the study: This film is an attention call to all surgeons involved in laparoscopic surgery explaining the main points to keep in mind in order to prevent this unpleasant complication, how it happened and the way we treated it.
Material and methods: A real time iatrogenic choledocal lesion during a laparorscopic cholecystectomy is presented. We specially focus on the clue points that we retrospectively consider necessary to know in order to prevent this unlikely complication, the way how we resolved it and our current data with all the complications that we have suffered.
Conclusions: An iatrogenic lesion of the biliary tract during a laparoscopic cholecystectomy may happen in any laparoscopic procedure with independence of the surgeon experience. Knowledge of the main points to prevent this lesion is mandatory, as well as the way to repair the biliary tract.

Transcylindrical cholecystectomy. A new technique for minilaparotomy

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Introduction: Laparoscopic cholecystectomy has become the treatment of choice for cholelithiasis, but needs to be learnt and requires expensive materials. Minilaparotomy is not without difficulties. We present an original technique for minilaparotomy cholecystectomy, which facilitates the procedure.
Method: This technique is based on the introduction of a 10¥3·8 cm cylinder with a protruding plug on one end, through which we performed the cholecystectomy. A right epigastric incision of the same size as the cylinder (i.e. 4·5 cm) is made. One then proceeds to introduce the cylinder towards the Calot's triangle. Removal of the plug, neck traction and the help of little gauzes to reject neighbouring structures reveal a well defined and stable field, where it is easy to dissect the hepatocystic triangle, section duct and cystic artery between clips and, finally, remove it from the liver bed. Dissection is carried out with endoscopic or conventional materials.
Results: We have operated with this technique on 117 consecutive patients. A postoperative hospital stay of 1·8 days. Average operation is 43 minutes. Incision had to be enlarged on 12 instances; one wound infection. We have not had any main biliary duct injury. Postoperative VC and FEV1 have been reduced to a similar level to that of laparoscopic cholecystectomy.
Conclusion: Trancylindrical cholecystectomy is a fast and safe technique, and it is less expensive than laparoscopic cholecystectomy.

See better, find more, be not (so) invasive! The proper postprocessing methods in the evaluation of the HCTCA

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Aim of the study: Among the investigation methods of bile ducts the HCTCA (Helical CT Cholangiography) is a relatively new, noninvasive imaging method.

Our experiences are based on more than 50 patients investigations by a spiral CT equipment.
Materials and methods: Hepatotrop contrast material has been adjusted intravenously in a long lasting infusion in order to reach reasonable opacification in the biliary system. The pictures have been taken in two delayed series (if necessary for the optimal filling, also in an additional one).

Because of the 3D reconstruction thin slices are recommended (2·5 mm).

After having the row data the pictures have been inspected by a normal mode each of the whole series has been evaluated by 3D rendering. Multiplanar reconstructions (MPR) have been made in all three dimensions and in any of the recommended supplementary planes. Maximum intensity projection (MIP) images have been reconstructed by subtracting the environment of the bile ducts. The spectacular and plastic shaded surface display (SSD) serves the better understanding for the surgeon.
Summary of results: In all cases, there was optimal opacification in the biliary tree. In 11 cases we found alterations intraductally, in 23 cases the reason of the disturbance was shown to be outside the biliary tract or the papill of Vater.
Conclusions: HCTCA is a very useful, noninvasive and tolerable tool for demonstrating the bile ducts and surrounding area. By using the proper method we can see little and even hypo-isodense stones intraductally, stricture or ligations on the biliary tract and anatomical variants. To apply the proper postprocessing method is important for getting relevant results.

The surgical technique of microlaparotomy cholecystectomy

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The conventional and laparoscopic cholecystectomy (LC) is as already every day utilized method, the operation procedure is well developed and the instruments used allow a reliable operation. The cholecystectomy performed by minilaparotomy is not yet a widespread procedure, the issue minilaparotomy has not been defined yet. The authors are demonstrating the surgical technique of microlaparotomy cholecystectomy (MLC) and the categorization of minilaparotomy. The gallbladder removal performed by abdominal incision less than 4 cm is via microlaparotomy, the 4–6 cm by modern mini- and the 6–8 cm via the conventional minilaparotomy cholecystectomy. For the success of operation a proper light source and the operative exposure are mandatory. In 2012 unselected cases operated for cholelithiasis and their complications, 92·5 per cent had MLC, 7 per cent required modern minilaparotomy, 0·3 per cent had classical mini and classical laparotomy. 17 per cent of the operations were termed as difficult. The majority of these were in the beginning as they found the best technique for the incisions and the exploration of the operative area, especially in obese patients. Inadequate lighting and exposure of the operating field were other factors. Also included are cases with difficult complicated pathology.

Acute emphisematous cholecystitis

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Acute emphysematous cholecystitis is a rare insidious and rapidly progressing disease that requires prompt surgical intervention.

The diagnosis is established usually when the plain abdominal X-ray shows gas within the gallbladder or in its wall.

It is important for the emergency physician to be aware of this clinical entity. The authors made a video showing the surgical approach, emphasizing the abdominal X-ray findings and ultrasound diagnosis.

Comments will be made during the video presentation and discussion after.

Turkish method: a safe, rapid method for laparoscopic cholecystectomy (610 cases)

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Today, reports have been focused mainly on technical changes proposed to prevent the complications of laparoscopic surgical procedures. These techniques are gaseless procedures against the complications due to CO_2 and open laparoscopic procedures against the complications of Veress needle and the trocars. In order to overcome these complications, laparoscopic cholecystectomy technique by using three ports (Hatay triangle points) and low intraabdominal pressure (4–8 mmHg) in which Visiport$^{\text{TM}}$ (USSC) have been used as the first trocar – Turkish Methods –, was developed in Dörtyol State Hospital in 1993–94; which has the advantage of both gaseless technique and open laparoscopic technique and also time saving. 610 patients operated by using this technique have been reviewed in a prospective study.

Among the patients; 480 were female (av. age 47·3), 130 were male (av. age 52·4). 72 patients had acute (11·8 per cent), eight patients had sclerosing chronic cholecystitis. 15 patients had previous upper abdominal operations. The mean duration procedure was 26·3 min for female patients and 41·6 min for male. Drains were used in 60 patients (26 female,34 male). Fourth tricar was necessary for 12 patients (2 per cent). Eight patients necessitated conversion (1·3 per cent). Five patients had urgent relaparoscopy in the first postop. week; two patients had bleeding, three patients had biliary peritonitis. None of these patients necessitated laparotomy and were successfully managed by laparoscopic homeostasis, lavage and drainage techniques. Six patients had incisional hernia in the late postop. period. No mortality was encountered in these series.

As a result, we concluded that: a) the points of Hatay triangle were suitable sites of placing the trocars; b) Visiport$^{\text{TM}}$ (USSC) maintained a safe and rapid way of insufflation; and c) 4–8 mmHg CO_2 was enough for laparoscopic cholecystectomy.

Laparoscopic posterior truncal vagotomy and anterior linear gastrectomy

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Introduction: Elective surgical treatment of duodenal ulcer has its indications. The laparoscopic approach offers clear advantages. We have carried out a laparoscopic approach using four truncal vagotomies with pyloroplasty, a posterior truncal vagotomy and seromyotomy and four posterior truncal vagotomies with anterior linear gastrectomy (PTV-ALG). In none of the cases of PTV-ALG existed symptoms of stenosis, the indication for surgery being poor response to medical treatment or episodes of upper gastrointestinal haemorrhage.
Material and methods: The patient is placed on the operating table in the supine position with 30° head-up tilt, with the surgeon between the legs of the patient. Five trocars are used, four of 10 mm placed in right midclavicular line, left anterior line, subxyphoid and upper middleline, where the optics of 0° is placed, and one of 12 mm in left midclavicular line. The dissection begins opening the pars condensa visualizing the right crura and opening the right phreno-esophageal space until location of the posterior vagal trunk. Section between clips of the vagal trunk. By means of three 3/0 silk stitches we mark 1- the starting point that includes the first branch of the crow foot, 2- the middle point near the lesser curvature and 3- the last once overcome the gastric fundus already in posterior face. The ALG is carried out by means of the successive application of endoGIA 30 helped with the tractors. We have needed between six and eight loads in order to complete the ALG.
Conclusions: Neither the time of evolution, or the number of cases are enough to allow any conclusions. Anyway, with more than a year of follow-up none of the cases have presented with ulcerous symptoms nor relapse.

A nylon guidewire for repeated oesophageal dilatations

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Conservative dilatation of oesophageal strictures (due to cancer, of corrosive ingestion, operative anastomoses) may be difficult, because of a tortous, kinked or very tight stricture canal or by atypical anatomical morphology. The introduced guidewire may get stuck, perforation is possible.

In the period 1975–1997 in 39 such patients with a difficult stenosis the authors applied a method with retrograde stricture dilatation and introduced nylon guidewire for long time repeated bougie dilatations.

Within a laparotomy and gastrotomy, up to the retrograde stricture dilatation, the wire was lead from the gastric lumen retrograde through the dilated stenosis to the throat and mouth or nose. The distal end of the wire through gastric and abdominal wall was fixed to the abdominal wall surface. The so introduced wire was later used as a guide for repeated dilatations. In nine patients the wire was used for over one year. Totally 135 dilatation procedures were performed. No complications related to the wire was observed. Transient clinical improvement was obtained in 22 patients and long lasting or permanent dilatation in 11. Technical details, clinical data of the patients, endoscopical and radiological documentation are presented by video.

A nylon guidewire installed for long duration can be used for repeated dilatations in difficult oesophageal stenoses.

Procedure of video assisted blunt dissection for patients with early esophageal cancer

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Introduction: After stripping or blunt dissection of esophagus, it is common that the substitute of esophagus is passed through the retromediastinum to protect after bleeding and leak of air. We developed mediastinoscope with transparent optical sheath for observation to the retromediastinum space after stripping of the esophagus.
Material and methods: Eight patients with sm-pm esophageal cancer were applied this methods. Stages were diagnosed by endoscopic-ultrasound and/or CT. Optical sheath was made by poly vinyl chloride (PVC) and 33 cm of length and 2·3 cm diameter. It is consisted to double lumen of large lumen (15 mm diameter) for mediastinoscope and small lumen (5 mm diameter) for suction. Using the transparent optical sheath with mediastinal scope, surrounding connective tissues is dissected along to the esophagus from cervical incision and abdominal hiatus.

Adter that, the esophagus is pulled out from cervical region to abdomen by using vein stripper. The transparent optical sheath with mediastinal scope is inserted again from cervical region to retromediastinum for observation this procedure under video assisted.
Results and conclusion: After removing esophagus, the retromediastinum could be observed and bleeding and/or injuries of pleura were clearly detected and appropriate manoeuvre could be done with video monitor. Operative duration and blood loss were remarkably decreased in comparison with conventional thoracotomy method. There was no complications and this technique might be useful and safe for patients who receive the blunt dissection for early stage esophageal cancer.

Total laryngo-oesophaguectomy plus bilateral radical cervical lymphadenectomy for the treatment of a carcinoma of the cervical oesophagus

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Introduction: Carcinomas of the cervical oesophagus usually have a bad prognosis and surgical treatment is difficult and extensive. Generally, curative procedures include en-block resections of neighbour organs.
Material and method: We present in this video the case of a 44-year-old male admitted with total dysphagia and 16 kg weight loss. The endoscopist found a stenotic tumour immediately above the vocal cords that needed dilatation to obtain a biopsy and showed an epidermoid carcinoma. CT scan defined the possible infiltration of the posterior wall of the trachea. Total parenteral nutrition was initiated a week before surgery.

En-block resection included a larynguectomy, thyroidectomy, total parathyroidectomy, bilateral radical cervical lymphadenectomy and transhiatal total oesophaguectomy. A gastroplasty via posterior mediastinum was chosen for the reconstruction making the anastomosis at the level of the pharynx and a very low tracheostomy was added.

The postoperative period was satisfactory. The patient needed oral support with thyroid hormone, calcium, vitamin D. Although calcium levels never raised above 6·5 mg/dl tetania episodes never occurred. Analysis of the specimen showed infiltration of the left thyroid capsulae and an only positive node belonging to the tracheo-oesophagic chain. Afterwards, adjuvant radiotherapy and chemotherapy was added.

Six months later patient weight was 48 kg and oral food intake was normal.
Conclusion: Carcinomas of the cervical oesophagus need aggressive surgical treatment even this may prove paliative. Short-term improvement of symptoms occurred in our patient, but further evaluation of results are to be made in the future.

Surgical treatment of achalasia by laparoscopy

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Introduction: In spite of the fact that pneumatic dilation of the cardia in achalasia offers some acceptable results, dysphagia, although diminished, usually reappears during the first months. We show a Heller myotomy associated with a Dor fundoplication in an achalasia patient, sent directly to surgery without previous dilation. The patient complained for year and half of progressive dysphagia and regurgitation, having lost 6 kg of weight. The X-ray study, endoscopy and manometry were compatible with achalasia, with tendency towards vigorous type and LESP at rest of 36 mmHg.
Material and methods: Five trocars of 10 mm were used, placed in right midclavicular line, left anterior axillary line, left middle clavicular line, subxyphoyd and upper middle line where the optics of 0° was placed. We carried out the complete dissection of the esophagic hiatus. Once dissected both crura, the esophagus was isolated creating a posterior window from right to left, surrounding it with a ribbon. At least about 7 cm of esophagus was freed identifying and peserving the anterior vagus. The myotomy was carried out with scissors without electrocoagulation and maintaining an intraesophageal bougie of 40F, beginning 2 cm below the gastroesophageal junction. We used the cardial artery like anatomical reference. The myotomy was prolonged upwards in about 6 cm being testing by intraoperative endoscopy its completion and the absence of perforation. We performed a partial fundoplication Dor type to avoid the gastroesophageal reflux.
Conclusion: The postoperative evolution was satisfactory. After one year the patient is totally asymptomatic without dysphagia, nor pyrosis. The manometry show a high pressure zone of 3 cm of length with 8 mmHg and a pHmetry without pathologic reflux.

Stomach

Intraoperatory and videoscopic aspects of the pharyngocolical anastomoses within the oesophagoplastical surgery for postcaustical high oesophagian stenoses

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The paper analyses the special aspects raised by four patients with postcaustical high oesophagian stenoses after their having taken caustical soda, with a high oesophagian total stenosis, two of them presenting also the burning of the epiglottis with a larynx stenosis (which needed traheostomy). After firstly having carried out a feeding gastrostomy with peritoneal collar – Gavriliu method, six months later we carried out an oesophagial by-pass with anizoperistalatic left colon, two with presternal colon and two retrosternally. The cervical anastomosis was carried out in the second stage, and, due to the oesophagian total stenosis, it consised of latero-lateral pharyngo-colonoanastomosis, with extramucous monolayer threads on the colon and total ones on the pharynx; in two cases the pharyngotomy has been carried out in the hyoid bone bed after its partial resection, and other two cases the pharyngotomy was carried out through a transverse incision, subhyoidal.

After a radiological and videoendoscopic control which noticed the cervical pharyngocolic anastomosis integrity, the feeding per os was resumed in two weeks, the gastrostomy was eliminated after other two weeks.

The postoperatory functional result was very good in all the four cases, the patients putting on weight, 5 to 25 kg within the first postoperatory year.

Laparoscopic surgery of the retroperitoneal organs

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A laparoscopic transperitoneal approach was used for the kidney and adrenal glands In the case of serous renal cysts, unroofing of the prominent dome was performed Seventeen patients were operated, 14 with right renal cysts and three with left ones. The diameter of the cysts ranged between 6 and 14 cm. Average operative time was 50 minutes. There were no incidents, nor postoperative complications.

Laparoscopic nephrectomy was performed in five cases, all for sclero-atrophic kidneys of inflammatory origin. There were three right and two left nephrectomies On the left side operation is more difficult due to close relation to the left colon and spleen. From the very beginning it is necessary to find and section the urether, because its proximal stump will serve for suspending the organ and as a guide to progress with the dissection towards the renal hilum. On the right side, for a better operative exposure, one must also perform a Kocher manoeuvre

One laparoscopic nephropexy, using a polyglactinic mesh after Hubners technique, was performed, for a right renal third degree ptosis.

Right adrenalectomy was performed in two cases for benign tumours, 4–5 cm in diameter and in one case for an adrenal cyst. Left adrenalectomy was performed in one case For a proper exposure of the adrenal gland and its middle venous pedicle on the right it is recommended to perform a partial duodeno-pancreatic mobilization. On the left, mobilization of the left colon and spleen are essential. Following these steps, blood loss was minimal and adrenalectomy much eased.

The most demanding operations were the nephrectomy and the nephropexy, needing between 3–5 hours to be completed. There were no postoperative complications, all patients being discharged cured.

Laparoscopic treatment of parahiatal hernias

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Surgery avoids the potential complications of large hiatus hernias The long incision of the classical abdominal and thoracic approaches are associated with pulmonary infections and slow recoveries. Laparoscopic surgery avoids these problems and offers a number of advantages. Our video shows three cases of the total of 10 patients that we have operated with laparoscopic technique.

Methods: We reduced the paraesophageal hernias and partially or completely resected the sack of three patients as we show in the video. Large diaphragmatic defects were repaired with non-absorbable sutures, no mesh was used The procedure ended with either a Nissen's or Dor fundiplication antireflux technique.

Results: Mean operating time was 90 minutes. Patients had oral tolerance to diet at 24 hours and left hospital on the fourth postoperative day. There was no case of relapse at six months follow-up.

Conclusions: Laparoscopic treatment of large paraesophageal hernias offers an excellent therapeutic alternative to open surgery; less infection, faster recoveries and shorter hospital stays. Fields of view of anatomical structures are better than open surgery.

Laparoscopic inguinal hernia repair using a totally extraperitoneal approach

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Totally extraperitoneal herniorraphy (TEP) probably is the best laparoscopic inguinal hernia repair technique because it is based on classic open preperitoneal procedure with the advantages of the laparoscopic approach

The peritoneum is kept intact, avoiding the potential risk of damaging intra-abdominal organs, pneumoperitoneum or vascular injury. Spinal anesthesia can be used.

Definitely, the TEP is a laparoscopic modification of Stoppa's open operation concerning a dissection and mesh placement, improving the approach and thus, giving better postoperative comfort.

We present the technical steps and the most important anatomical references 1) Dissection balloon is used to facilitate preperitoneal space dissection. 2) Two 5 mm trocars in abdominal middle line are placed. 3) Anatomical dissection landmarks. Cooper ligament, epigastrics vessels to know the type of hernia; iliopubic tract, inguinal internal ring, psoas. 4) Dissection of the elements of the cord avoiding missed indirect hernial sac, the most important cause of recurrence during the learning curve (retained recurrences). 5) The mesh is introduced through the 10 mm umbilical trocar and positioned over the entire musculopectineal orifices with sufficient overlap at the medial and lateral borders. The size is 14 × 11 cm without cuts. 6) The helicoidal stapler is used to fixate the mesh.

Flexible choledochoscopy: technical improvements and indications

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The choledocoschopy (CD) represents the only exploration that allows a direct view of the intra and extrahepatic biliary tract, with a 75–85 per cent sensitivity and 100 per cent specificity in diagnosis of neoplasms and lithiasis. It reduces the retained stone rate from 9–14 per cent to 1–3 per cent. We adopted the CD with a flexible instrument, 4-6 mm in diameter, as the routine exploration of the biliary system when the preoperative studies or intraoperative evaluation suggest biliary pathology. It could or could be not preceded by intraoperative cholangiography. We can also make biopsies and remove stones through the work channel The CD can be done through a choledochotomy or the cyshie duct given a previous balloon dilatation. The procedure lasts an average of 20 minutes and needs the continuous perfusion of normal saline solution at a pressure no higher than 100 mmHg. The CD is connected to the laparoscopic camera and the images are seen on the video screen We present six patients with different diseases who demonstrate the usefulness of the procedure There was no morbidity related to the procedure We saw a significant improvement in the number of primary closure of the bile duct since we started the CD. We were not able to complete the CD with the laparoscopic approach. The most important technical problem that occurred was when we tried to visualize the hepatic confluence, because of the extension of the common wall between the cystic duct and the common hepatic

Pediatric endoscopic surgery

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The minimally invasive procedures are now being successfully applied to pediatric surgical procedures such as cholecystectomy, cryptorchidism, diagnostics of inner genitalia, peritonitis, thoracosopy.

The anticipated benefits of these techniques include less postoperative pain, shorter hospital stay, and lower hospital costs, with a quicker return to normal activity. Obviously, a number of precautions should be taken in children: the use of open laparoscopy seems the main point.

This video (30 mn) shows the main indications of laparoscopy in childhood: appendectomy, gastroesophageal reflux, abdominal cryptorchidism, ovarian cysts, splenectomy, nephrectomy and thoracoscopy.

Laparoscopic operation of double-splitting hiatal hernia

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Introduction: The method of laparoscopic repair of hiatal hernia is accepted in surgery.

Methods: Between January 1994 and December 1998 authors have done 125 laparoscopic operations. They would like to demonstrate the most difficult hiatal reconstruction, where they have treated a large hiatal hernia. The three-fourth of the stomach was in the thoracic cavity partly through the hiatus and partly through the right ruptured crus itself. The authors demonstrate their procedure and the use of Harmonic Scalpel.

Results: During their operation they did not have any secondary injury. There was no need for tranfusion. Their patient was completely pleased with the results after discharge, still is under regular control. In the demonstrated rolling-hernia operation the advantages of Harmonic Scalpel were: clean, bloodless operating field; easy and safe transsection of vessels and tissue; shorter operation time.

Conclusion: Based on their experiences and on the data of literature the laparoscopic technique is a feasible method in the treatment of hiatal hernia.

Laparoscopic reoperation after laparoscopic hiatal reconstruction

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Introduction: The laparoscopic hiatal reconstruction is accepted treatment of hiatal hernia. In cases of recurrent hernias the accepted treatment mostly is the open reoperation that means the reconstruction of the incorrect hiatus and fundoplication.

Methods: A 68-year-old woman was operated for paraesophageal hiatal hernia. Laparoscopic hiatal reconstruction with Nissen fundoplication was performed. She developed a recurrent paraesophageal hernia. We performed a re-laparoscopy and we realised tearing of the crural stitches, opening of the hiatus and hernialisation of the fundus of stomach. A laparoscopic hiatal reconstruction and Toupet fundoplication was performed.

Results: The hernia was withdrawn, the hiatus was correctly closed, the fundus was fixed and the fundoplication was performed entirely laparoscopically. There was no intraoperative complications. Operation time was 65 minutes. The postoperative course was uneventful, and radiologic examination showed lack of hiatal hernia. Six months later our patient has no complaints.

Conclusion: The treatment of failed laparoscopic hiatal reconstruction generally requires reoperation. Open procedure is recommended to make a correct solution. In special cases during laparoscopic reoperation (re-laparoscopy) reconstruction of hiatus could be performed with success.

Laparoscopic treatment of perforated peptic ulcer: first experience

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It is accepted that emergency treatment of perforated peptic ulcer is based on the surgery, namely simple closure or more definitive ulcer surgery. The preliminary results of laparoscopic treatment of 11 patients with peptic ulcer perforation are reported here.

For patients with perforated peptic ulcer, without ulcer history, we perform laparoscopic duodenorrhaphy with omental patch repair. We used this method in 11 patients. Ten of them were males (age from 20 to 41 years). Mean time from perforation until operation was 7 hours 42 minutes (range 3–15 hours). The perforation of duodenum ulcer with serofibrinous peritonitis was found during laparoscopy in all cases. Ulcers were sutured by vicryl sutures. Additional sutures with omental patch were passed to surround the perforation. This was followed by peritoneal lavage with normal saline. At the end of operation the tubes under the liver and in pelvis minoris were left. The operation lasted for a mean time 75 minutes (range 40–135 minutes). For the protection of duodenal suture, in the case of big perforation hole (0·8 cm), nasograstric tube was left for two days in two of the operated patients.

Next day postoperatively all patients started to walk, only non-narcotic analgetics were applied. No leakage was demonstrated and no postoperative complications accrued. No conversions were needed in our practice. The mean hospital stay was 7·9 (range 7–14) days.

One month later, during control fibrogastroduodenoscopy, healed ulcer scars were found, no gastric evacuation disorders were demonstrated.

Conclusion: The laparoscopic surgery of perforated peptic ulcers is effective in the first hours after perforation.

Operating technique and early results of endoscopic subfascial division of perforating veins

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Introduction: Direct surgical ligation of incompetent perforating veins has been reported to effectively treat severe chronic venous insufficiency. Although it could be associated with significant wound complications. We present our operating technique and early results of endoscopic subfascial division of the perforating veins.

Materials and methods: From July 25, 1996 to December 31, 1997, 27 legs in 21 patients (12 female, 9 male) were treated with endoscopic subfascial division of perforating veins. Seventeen of the 27 legs had active or recently healed venous ulcers. Mean duration of the ulcerations was 7·3 years. Standard laparoscopic equipment with two 10-mm ports was used to perform clipping and division of medial perforating veins through two small incisions made just below the knee, avoiding the area of ulcer. Carbon dioxide was insufflated at a pressure of 30 mmHg into the subfascial space to facilitate dissection, and a pneumatic thigh tourniquet (300 mmHg) was used to obtain bloodless operating field. Additional removal of superficial veins was performed in 17 limbs.

Results: A mean of 4·1 perforating veins (range 1–6) were divided; tourniquet time averaged 45 minutes (range 30–110). We observed no wound infection. Superficial thrombophlebitis was an early complication and occurred in one patient. In 22 legs the ulcer healed and symptoms resolved. In three legs the ulceration improved and in two it was unchanged.

Conclusions: Endoscopic subfascial division is a safe and precise technique avoiding skin incisions in the ulcer area. This method allows us to reach all of the medial perforators. It could be used successfully in management for patients with most severe forms of active or healed venous ulcers.

Gasless laparoscopic cholecystectomy with mini-instruments (2 mm) video

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Gasless laparoscopy, in which abdominal distension is provided by an abdominal wall lifting device, has been our choice for patients undergoing laparoscopic surgery. Cholecystectomy has been performed in 450 successive patients with good results. Recently, we started practising this type of operation using instruments with 2 mm of diameter. The video demonstrates, step by step, the possibility of performing a cholecystectomy with three ports of 2 mm and a fourth one periumbilical of 10 mm parts Using gasless technique (we will show the abdominal wall lifting device – Laparolift®, Origin Medsystems – which is necessary to produce the working chamber) we achieved a very good vision and an excellent exposure of the cystic duct, the artery and the common bile duct. As usual with this technique, irrigation and suction were very helpful and the 2 mm suction device made the dissection of the triangle of Calor very easy to perform. The laparoscope and the endoclip applier were introduced through the periumbilical port, which was also utilized to remove the gallbladder.

For cholecystectomy we usually insert only three trocars (one 5 mm and two 10 mm). However, we consider advisable to insert a fourth port, when using smaller instruments, to make surgery more comfortable and safer

Laparoscopic truncal vagotomy and antrectomy (video)

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We present a video demonstrating that Laparoscopic Truncal Vagotomy and Antrectomy can be safely carried out without CO_2 pneumoperitoneum. We performed this operation in a patient with four recurrences of gastric ulcer after medical treatment and maintenacne therapy Preoperative work-up included upper endoscopy with target biopsy of the edge.

In order to perform the operation we used, as usual, an abdominal wall lifting device (Laparolift®, Origin Medystems) which is necessary to produce the working chamber The operation was carried out according to the classic steps of truncal vagotomy and antrectomy (Billroth II, antecolic), but under gasless laparoscopic surgery. Unstressed access to the patient and clear visualisation of the anatomy is possible with gasless technique which is compatible with the use of conventional instruments which make surgery easier. The technique greatly reduces potential patient morbidity associated with CO_2 pneumoperitoneum, particularly pneumothoraces and emphysema Anaesthetists report little difficulty performing their duties.

The use of ultrasonic energy in the laparoscopic cholecystectomy

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Aim: The aim of this study is to demonstrate our experience on the use of the ultrasonically activated scalpel (UAS) in the laparoscopic cholecystectomy (L.C.).

Methods: Between January and December 1997 the UAS was applied in 240 patients who underwent L.C. (164 females, 76 males, mean age 56·5 years) Local findings during the operation were: 180 uncomplicated cholelithiasis, 22 acute cholecystitis, 17 gallbladder empyema, 13 hydrops, eight lithiasis with liver cirrhosis of Child-stage A and B (3·3 per cent)

Results: There was one conversion to open procedure, but not due to the UAS. The mean operative time after the first 10 procedures was 15 min (5–33 min), in average 4 min shorter than with electrosurgery The incidence of gallbladder perforation from the device itself was one per cent The mean length of postoperative hospital stay was 2·5±0·5 days. There was significantly less fluid amount from the drain in comparison with patients operated with electrosurgery The complete technique is demonstrated in the video tape.

Conclusions: The experienced advantages of the UAS in the L.C. over electrocautery can be summarized as following:

1. Safe and effective hemostasis, especially needed in cirrhotic patients
2. Minimal tissue injury and low incidence of Gallbladder perforation during dissection with the device.
3. No risk of inadvertent distant injury resulting from arcing and sparking
4. No smoke generation and clear visual field.
5. Reduced operative time
6. No need for patient grounding
7. No use of dissector and scissor. The procedure can be carried out with the use of the UAS alone and this reduces significantly the cost
8. Drainage can be avoided in most of the cases.

The laparoscopic extirpation of a wandering spleen

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A 79-year-old female patient with chronic lymphatic leukemia since 1971 was presented with a severe relapse of autoimmune thrombocytopenia. The patient already underwent an irradiation of the spleen with a maximum dose of 24 Gray Now the thrombocytopenia was resistent to medical therapy with leukeran, corticosteroids and immunoglobulins. As further irradiation was not possible, splenectomy was considered On preoperative computed tomography scan of the abdomen the spleen was localized in the left fossa and hypogastrinum. The total length of the spleen was 14·7 cm. The ectopic spleen with a weight of 885 gramme was successfully removed by the laparoscopic approach. Histopathology revealed invasion of the spleen by CLL. After the splenectomy normalization of the thrombocytes occurred (250 000 on the day of discharge).

The laparoscopic marsupialization of a giant post-traumatic cyst of the spleen

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A 26-year-old female patient was transferred from the gastro-enterology department with a history of increasing pain in the left upper quadrant of the abdomen. Sometimes there was irradiation of the pain to the left thoracic region or to the left fossa Furthermore, there were complaints of weariness and shortness of breath in doing daily activities. On abdominal examination a spherical mass was felt in the left upper quadrant. Echography of the abdomen showed a thin walled cyst with homogeneous content and a diameter of 140 mm Computed tomography scan of the abdomen showed a giant splenic cyst with a cross sectional diameter of 17 cm and a height of 16 cm A laparoscopic approach was proposed with further decision making based on the frozen sections during the operation. A successful laparoscopic marsupialization was performed.

Laparoscopic Nissen-Rossetti fundoplication

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The surgical treatment of the gastroesophageal reflux represents a clear indication for a laparoscopic approach. The laparoscopy allows the same surgical technique diminishing the surgical trauma.

From November 1992 to December 1997 we have performed this technique in 92 patients. The surgical technique was similar in all the cases although with the learning curve the operative time declined from 4 to 1·5 hours, the mean of the series 134 minutes. Five trocars of 10 mm are used, right hypohondrium, left anterior axillary line, left middleclavicular line, subxyphoyd and upper middle line for the optics of 0°. We begin the dissection opening the pars condensa, visualising the right crura and opening the phreno-esophageal space. Once dissected both crura, we carry out the isolation of the esophagus creating a posterior window by dissecting right to left. Later on, we complete the dissection of both cruras, and liberate the His angle and the gastric fundus without section of the short gastric vessels. In all the cases we carried out a crura repair, with one to four stitches. In 89 cases we carried out a short Nissen-Rossetti fundoplication of about 2·5–3 cm, with three sutures, using the anterior face of the gastric fundus to perform a valve without section of short gastric vessels. In 64 cases we used a 50F intraesophageal bougie for calibration. In two cases we carried out an anterior fundoplication Dor type, in one for technical reasons and in the other for manometric contraindication to complete fundoplication. In the last 32 cases the valve was sutured to the right crura to avoid a torsion effect. In a case conversion to open fundoplication for haemorrhage was necessary. Cholecystectomy was associated in 14 cases.

Operative strategy in laparoscopic splenectomy

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Introduction: The laparoscopic splenectomy is suitable in spleens of less than 20 cm in length, and especially when it is possible their fragmentation for extraction as ITP and spherocytosis.

Material and methods: The placement of the patient is in supine decubitus with 30° head-up tilt and about 45° right lateral tilt. The surgeon stands between the legs of the patient. Four trocars, three of 10 mm and one of 12 mm, are positioned in middle line under xyphoyd, between umbilicus and xyphoyd, anterior axillary line subcostal (0° telescope) and middle axillary line subcostal (12 mm). In the last four cases the patient was placed in the lateral decubitus position. The dissection begins in the inferior pole of the spleen, liberating the splenic angle of the colon and, isolating and dividing between clips the vascularization of the inferior pole. The inferior pole is rised, sectioning the renalsplenic ligament and the fatty tissue of the inferior border of the hilius. We continue cephalad by opening the anterior face of the gastrosplenic ligament and dividing between clips the short gastric vessels. Later on, maintaining the spleen rised, we continue with the liberation of the renalsplenic ligament up to identify the hilar vessels isolated from the pancreatic tail, proceeding to their section with endoGIA. The liberation is finished with the section of the splenophrenic ligament. Later on, the spleen is introduced into a plastic bag. The bag is closed by tightening the pursestring at its top and is partially pulled out of the abdomen through the 12 mm trocar. The spleen is morcellated within the bag and removed.

Conclusions: During the last three years we have operated on with this technique 18 patients. In a case, the first of the series, it was necessary the conversion to laparotomy for haemorrhage and another case was reoperated in the postoperative period. In a case we associated a cholecystectomy.

Laparoscopic posterior truncal vagotomy and anterior linear gastrectomy

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Introduction: Elective surgical treatment of duodenal ulcer has its indications. The laparoscopic approach offers clear advantages. We have carried out a laparoscopic approach using four truncal vagotomies with pyloroplasty, a posterior truncal vagotomy and seromyotomy and four posterior truncal vagotomies with anterior linear gastrectomy (PTV-ALG). In none of the cases of PTV-ALG existed symptoms of stenosis, the indication for surgery being poor response to medical treatment or episodes of upper gastrointestinal haemorrhage.

Material and methods: The patient is placed on the operating table in the supine position with 30° head-up tilt, with the surgeon between the legs of the patient. Five trocars are used, four of 10 mm placed in right midclavicular line, left anterior line, subxyphoid and upper middleline, where the optics of 0° is placed, and one of 12 mm in left midclavicular line. The dissection begins opening the pars condensa visualizing the right crura and opening the right phreno-esophageal space until location of the posterior vagal trunk. Section between clips of the vagal trunk. By means of three 3/0 silk stitches we mark 1- the starting point that includes the first branch of the crow foot, 2- the middle point near the lesser curvature and 3- the last once overcome the gastric fundus already in posterior face. The ALG is carried out by means of the successive application of endoGIA 30 helped with the tractors. We have needed between six and eight loads in order to complete the ALG.

Conclusions: Neither the time of evolution, or the number of cases are enough to allow any conclusions. Anyway, with more than a year of follow-up none of the cases have presented with ulcerous symptoms nor relapse.

Laparoscopic pericystectomy with the harmonic scalpel for hepatic hydatidosis: case report

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In this videoband, we present a case of hepatic hydatidosis treated by pericystectomy with the aid of the 'harmonic scalpel' apparatus (Ethicon).

The patient was a 47-year-old man with a computerized tomography revealed Gharbi grade III exophytic lesion (8 × 6 cm) at segment III. At the laparoscopic exploration, the cyst was found to be covered with omental adhesions which were divided with the aid of 'harmonic shears'. The cyst was removed by cutting in the plane between the cyst and hepatic paranchyma in the coagulation mode of the apparatus at full energy. Two hepatic ven branches (1–1·5 mm) and an arterial branch (1 mm) were observed as disting structures and secured with clips. At the end of the procedure, there was only minimal bleeding from the liver surface and this was controlled with the argon beam coagulator. Then the cyst was placed into a plastic bag and extracted after the cyst contents were partially removed. The postoperative course of the patient was uneventful. He was discharged after two days.

The harmonic scalpel greatly facilitates the procedure by sealing the 'raw' liver surface effectively, i.e. there was no leakage of bile and only minimal bleeding. With the aid of 'harmonic scalpel' or a similar apparatus, pericystectomy can be conveniently added to the armementarium of the laparoscopic surgeon. This operation should be performed in the institutions with extensive experience in both laparoscopic and hepatobiliary surgery.

Oesophageal epidermoid carcinoma: results of surgery after neoadjuvant radiochemotherapy

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While surgery still remains the treatment of choice for oesophageal epidermoid carcinoma, there was no improvement of the survival rate in the past decades with 18 per cent five years actuarial survival. The aim of this study was to evaluate the interest of surgery after neoadjuvant radiochemotherapy to 1) increase the resection rate, 2) improve the actuarial survival rate, 3) increase the disease free survival (DFS), 4) avoid mutilating surgery. From February 1987 to September 1997, 55 patients (49 men and six women) with a mean age of 58±8 years (from 77 to 38) received oesophageal resection after neoadjuvant treatment. In eight cases there was a previous history of ENT epidermoid carcinoma. Tumour location was: upper 1/3 $n=19$, middle 1/3 $n=22$, lower 1/3 $n=9$ and double localisation in upper and lower 1/3 $n=5$. Impassable stenosis was observed in 20 cases. Thirty-five patients had endosonography, and tumour classification was mainly uT3 $n=25$ (45·5 per cent), uT4 $n=6$ (11 per cent) and uN1 $n=25$ (45·5 per cent), uN2 $n=6$ (11 per cent), the other patients were: uT0 $n=1$, uT1 $n=1$, uT2 $n=4$, uTx $n=3$, uN0 $n=5$, uNx $n=4$. Neoadjuvant treatment included two courses of chemotherapy 5-Fluorouracil (1 g/m^2/day) and Cisplatin (25 mg/m^2/day) from day 1 to day 5, and from day 21 to day 26 where half dose of 5FU was given. Radiotherapy was done from day 21 to day 36 giving a total of 36 grays. Full neoadjuvant treatment was possible in 67·3 per cent of cases, radiotherapy was completed in 85·5 per cent, and uneventful course was achieved in 56·4 per cent. Surgery was performed one month after the end of radiotherapy (at day 60). Tumour resectability was 96·4 per cent, only two patients had surgical exploration without tumour resection. Complete (curative) resection was achieved in 45 cases (82 per cent), and in eight cases (14·5 per cent) palliative resection was done. Forty-seven patients had gastroplasty and two had coloplasty. Three field lymphadenectomy was done in 38 cases (69 per cent) and two field lymphadenectomy in 15 cases (27 per cent). Operative mortality was nil, and hospital mortality was 7·3 per cent. The postoperative course was uneventful in 45·5 per cent of patients, complications that occurred were mainly pulmonary (34·5 per cent) and recurrent nerve palsy (23·6 per cent). Pathological tumour classification (AJCC 1988) was: Stage 2a $n=6$, Stage 2b $n=3$, Stage 3 $n=8$ (14·5 per cent), Stage 4 $n=13$ (24 per cent), and in 23 cases (42 per cent) the tumour was totally (or almost) sterilised (R±). Larynx preservation was achieved in 10 of 12 patients with theoretical indication of total pharyngolaryngoesophagectomy. The overall actuarial survival rate was 27 per cent and 22 per cent at four and nine years. The DFS was 28 per cent and 25 per cent respectively. Sixteen patients died with local or metastatic recurrence, and 19 are living (17 are disease free and two with metastasis). In the group R±, the actuarial survival rate was 53 per cent and 46 per cent at four and nine years, and the DFS was 46 per cent and 47 per cent respectively. Six patients died without recurrence and 12 are living and disease free. Neoadjuvant treatment is well tolerated by almost all patients when carefully selected. It appears that this combination therapy increases tumour resectability, it can allow in some cases laryngeal preservation. Significant improvement of the actuarial survival rate and DFS is observed in the R± group.

Antroduodenal motility in patients with gastroesophageal reflux disease and gastric symptoms

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Background: A considerable percentage of patients with gastroesophageal reflux disease present with gastric symptoms in addition to typical reflux symptoms. The underlying motility of the stomach and/or duodenum is poorly understood.

Aim: To characterize antroduodenal motility in patients with GERD and gastric symptoms.

Material and methods: Thirty-four patients (25 male, 9 female, age 25–78 years) with increased esophageal acid exposure on 24 hour esophageal pH monitoring (DeMeester score >14·7) and 38 healthy volunteers underwent 24 hour ambulatory antroduodenal manometry studies. The majority of patients (85 per cent) presented with gastric symptoms (nausea and vomiting, fullness, early satiety) in addition to typical reflux symptoms, the others had an increased Bilirubin exposure of the stomach and/or delayed gastric emptying. The total number and the duration of complete interdigestive motor cycles (IMC's) was analysed. The contraction frequency in the antrum and duodenum was calculated for the total, upright, supine and postprandial study period. Results were compared with the data of the 38 healthy volunteers.

Results: GERD-patients showed a lower total number of interdigestive motor cycles (IMC's) in the antrum and duodenum when compared to healthy volunteers (table). The postprandial contraction frequency in the antrum and duodenum was lower than in normal controls (table).

		Antrum			Duodenum		
		Control	GERD	*P*	Control	GERD	*P*
IMC	number/24 h	5	3	<0·05	8	4	<0·01
	duration (min)	120	122	n.s.	65	76	<0·05
Frequency	total	1·13	0·83	<0·01	1·82	1·93	n.s.
	upright	1·38	1·33	n.s.	2·12	1·86	n.s.
	supine	0·65	0·33	<0·01	1·11	1	n.s.
	postprandial	1·74	0·96	<0·05	4·68	3·22	<0·01

Values indicate median.

Conclusion: Patients with gastroesophageal reflux disease and gastric symptoms have reduced foregut motility which could compromise the outcome after antireflux surgery.

Scintigraphic findings correlate with symptomatology in esophagoplasty function evaluation

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Background: Esophagoplasty is nowadays a well-established surgical procedure for palliation or cure of malignant as well as benign esophageal disease. Apart from the underlying disease, quality of life depends on long-term functional results. Scintigraphy is a relatively simple well tolerated method of esophagoplasty function evaluation.
Material and methods: Thirty-one patients having undergone esophageal resection and substitution (n=24, 77·4 per cent) or bypass (n=7, 22·6 per cent) have been studied 3–186 months after the operation. Data concerning kind of operation, nutritional state, ability to swallow and symptoms as vomit, a feeling of 'fullness' or 'spasm' have been recorded. The patient was examined fasting for at least six hours. 1 mCi of 99 mTc sulfur colloid in 10 ml of tap water were given orally and the patient was instructed to swallow it at once and not swallow his saliva for 32 seconds. Examination was performed in supine position before and after taking sitting position, so that the role of gravity could be estimated.
Results: Transit time of 30 per cent of radioactivity exceeded 1312 seconds in 83·9 per cent of cases. 32 seconds clearance ranged from 3·12 per cent to 58·69 per cent. Even the best results of substitute transit and clearance were statistically highly significantly worse than the ones of a group of healthy volunteers. Best functional results have been observed in patients with jejunum or iso- or antiperistaltic gastric tubes. Substitute clearance due to gravity was the main contributor to overall clearance, especially in cases of whole stomach, and correlated well with present nutritional state (percentage of ideal weight). Scintigraphy was specific but not sensitive in revealing reflux to the substitute causing symptomatology.
Conclusions: Scintigraphy is a well-tolerated non-invasive method of screening patients after esophagoplasty for estimation of long-term functional results. Gravity plays cardinal role in food passage through esophageal substitutes, though differences between different parts of GI tract do exist and should be attributed to motility. Esophageal substitution with jejunum or iso- or antipersistaltic gastric tubes has yielded best functional results.

Multi-stage tracheo-bronchial stenting and esophageal intubation for malignant respiratory tract and esophageal stricture

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Successive airway stenting and pull-through esophageal intubation for combined malignant respiratory tract and esophageal involvement is presented. From 1982 to 1998 239 patients underwent palliative esophageal intubation with a personally designed, composite tube at our service. In 118 instances the secondary esophageal strictures were induced by primary or recurrent bronchial tumour and mediastinal tumour or metastases. Among them four patients having a stenosing tracheal or bilateral main stem bronchial carcinoma has been managed by endoscopically introduced Dumon tracheal or bronchial stent followed by in second-stage, our esophageal tube insertion with a limited invasive surgical intubation technique. The overall hospital mortality was 9·3 per cent, without surgical or pulmonary complication in the above mentioned group of patients. Stenotic malignant tracheobronchial invasion was considered previously as a main contraindication of the palliative esophageal intubation. Recently, airway stenting combined with esophageal intubation may be considered an important step for extended, complex palliation in this high risk group of patients.

Quality of life and function of the esophageal substitute after esophagectomy and esophago-gastrostomy for esophageal cancer

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The recently proposed Gastrointestinal Quality of Life Index (GIQLI)[1] was used to evaluate the outcome of subtotal esophagectomy and gastric pull-up in 45 consecutive patients (33 male, 12 female, median age 64 years), at a median 13 months after surgery. All the patients were recurrence-free; patients with anastomotic stricture were excluded. The GIQLI was based on a questionnaire containing 36 questions, each of which was attributed a score from 0 (=always) to 4 (=never), regarding foregut symptoms (heartburn, regurgitation, dysphagia, belching), as well as physical, emotional, social and therapeutic aspects of post-operative life in these patients. A matched group of 71 healthy subjects (41 male, 30 female, median age 61 years) served as controls. A subset of 15 patients (7 male and 5 female, median age 64 years), 10 with moderate to severe foregut symptoms and five with no symptoms, was also evaluated by means of endoscopy with esophageal and gastric biopsies, supra-anastomotic esophageal pH- and bilirubin monitoring (Bilitec®), gastric bilirubin monitoring, biliary scintigraphy with ^{99m}Tc-HIDA and gastric emptying scan of a semi-solid meal.
Results: The overall GIQLI score did not differ between patients and controls (120·5, r. 92–142, vs 127, r. 86–143, P=ns); however, the partial 'symptom' score was lower in patients than in controls (16, r. 9–20, vs 20, r. 12–20, P<0·05): 17 out of the 45 patients (38 per cent) were considered as having moderate to severe foregut complaints (sympton score ≤15). The partial score regarding the patient's physical status also differed from controls (P<0·04), whereas the emotional, social and therapeutic scores were similar in patients and controls. In the group of patients who underwent functional evaluation, the presence of esophagitis, gastritis and abnormal acid gastro-esophageal reflux did not differ between symptomatic and asymptomatic patients, whereas the percentage time of the presence of bilirubin in the intrathoracic stomach and in the esophagus was significantly higher in symptomatic patients (P<0·01): in particular, an abnormal esophageal exposure to bilirubin was found in eight symptomatic patients, but only in one asymptomatic case (P<0·05). An abnormal ^{99m}Tc-HIDA biliary scintigraphy and delayed gastric emptying tended to be more frequent among symptomatic patients, though the difference did not reach statistical significance.
Conclusion: The overall quality of life in patients who undergo subtotal esophagectomy and intrathoracic esophagogastrostomy for esophageal cancer is good and does not differ from that of healthy controls, although physical performance is impaired and some foregut symptoms are recorded. These symptoms seem to be mainly related to the presence of bile reflux and, possibly, to abnormal gastric emptying.

[1] Eypasch E, *Br. J. Surg* 82: 216–222, 1995.

Development of minimally invasive direct access surgical technology (MIDAST)

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The development of soft tissue microsurgery, precision minimally trauma surgery, endoscopic microsurgery and the application of video technology in 1960s and 1970s led to the new concept of Minimally Invasive Direct Access Surgical Technology (MIDAST) in the late 1980s. The MIDAST concept and instrumentation allows the surgeon to perform three dimensional-stereoscopic surgery now in eight subspecialities of surgery through a shorter incision. The incision is about 1/4–1/3 of the classic surgical incision. Special rectractor endoscope – JAKOSCOPE was developed from 1988 step by step until the final design was reached. Three sizes of Jakoscopes are available. High intensity fibre optics lighting provides brilliant visualization of the surgical area which is viewed by the surgeon's two eyes (binocular vision). Angled hand instruments have also been developed which give the surgeon better, direct access to work at the surgical site. He also has direct access for palpation and placing sutures or clips.

Modern versions of surgical stapling devices – the first surgical stapler was invented in 1907 by H. Hull in Budapest – are also useful for certain procedures. While the surgeon needs no video for the operation, an optimal specially developed video camera provides for demonstration and recording.

Most of the surgical procedures of MIDAST were developed in recent years experimentally and clinically by Hungarian surgeons. It has certain advantages over laparoscopic surgery such as expense, shorter operating time, no CO_2 gas insuflation needed. It is a real three dimensional approach which is easy to learn for an otherwise skillful surgeon.

By the turn of the century now, it is practised in general, cardiac, thoracic, vascular, pediatric, gynecological, urologic and orthopedic surgery.

Microlaparotomy cholecystectomy

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Starting in 1988, a new concept, surgical technique and instrumentation was developed to perform cholecystectomies through a 4 cm incision. The vertical midline incision is made at the base of the infrasternal triangle.

This minimally invasive direct access surgical technique (MIDAST) is comparable to the laparoscopic technique as far as the postoperative pain and ambulation but has more advantages.

For 1990 in unselected cases, all operations were started with a 4 cm microlaparotomy incision. Out of 2012 operations, 1861 cases (92·5 per cent), the 4 cm microlaparotomy incision was used. One hundred and forty-three cases (7·1 per cent) required modern minilaparotomy extending the incision up to 6 cm. The extended incision was required in cases of choledocholithotomies, repair of bilioenteric fistulas, anomalic location of the gallbladder, etc. In four cases (0·2 per cent), the incision was extended to 8 cm, i.e. classic minilaparotomy was performed. These included type II Mirizzi syndromes and sphincterolithotomy. Only four cases of 2012 required classic cholecystectomies through a modified longer than 8 cm incision. These cases included severe cystic artery bleeding and liver resection for gallbladder cancer.

The operated patients were grouped into three categories: 512 cases (25·5 per cent) simple; 855 cases (42·5 per cent) intermediate; 645 cases (32 per cent) obstructive cholecystitis. Three patients (0·014 per cent) died within 30 days after surgery. Ten patients (0·5 per cent) required reoperations, three for injury of the common duct, three bile leakage, three bleedings, one Schloffer tumour, one clip removal, one ileal intussusception. In 130 cases (6·5 per cent), stone was removed from the common duct through a 6 cm minilaparatomy incisions or in 31 patients (24 per cent of 130) through 4 cm microlaparotomy incisions.

Three hundred and forty patients (16·8 per cent) were classified as difficult surgery cases. The average operating time in the simple group 512 cases (25·5 per cent) was 18 minutes, in the intermediate group 855 cases (42·5 per cent) 35 minutes and in the obstructive cholecystitis group 645 cases (32 per cent) 30 minutes.

Minimal and direct access abdominal surgery with the 'Jako-endoscopic-retractor'

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In recent years, minimally invasive operations in abdominal surgery, due to laparoscopic techniques, has had a rapid development. A multi-purpose reactor system, the Jakoscope® developed by Jako provides an interesting alternative for minimal and direct access surgery without pneumoperitoneum. This instrumentation allows a direct access through 3–6 cm single incisions using fibre optic light.

During the past six months we used the Jakoscope® for several abdominal operations. We started first using it for cholecystectomies in previously operated patients (n=5) and two patients with contraindications for pneumoperitoneum. The mean operation time was 65 minutes (55 to 81) with success in all and the mean incision was 5 cm, intraoperatively measured. The average hospital stay was comparable to laparoscopic surgery as well as the average use of analgetics.

Encouraged through these results we operated on posterior rectopexy in two patients using 6 cm incisions. The average operation time was 63 minutes and the patients left the hospital after six days without problems and no anal prolapse.

With the rapid development of laparoscopic operating techniques other potentially minimal invasive methods have been neglected. Reducing operating times and analgesia, the cosmetic cut size and reduced hospitalization are positive results of the minimal and direct surgery with the described system. This new interesting surgical concept provides direct three-dimensional vision and palpation. The cuts are not longer than laparoscopic surgery when added. We are planning to operate a diverticulitis patient in the near future.

Aortoiliac reconstruction using minilaparotomy approach: technique and clinical results

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Aim: The large transperitoneal approaches used to the conventional aortoiliac reconstruction are accompanied with a relatively high postoperative morbidity and mortality rate (2 per cent to 5 per cent) even in patients who are good risks undergoing aortic surgery. This significant perioperative morbidity is partly caused by the major surgical trauma. To decrease the surgical stress on these patients the authors developed a less extensive procedure utilizing minilaparotomy and videoendoscopy.

Methods: From June 1993 through August 1997, patients undergoing surgery for aortoiliac occlusive disease were randomized comparing the minilaparotomy (ML) with conventional transperiotneal (CT) incision for aortic surgery. One hundred and nine patients participated in this trial, with 54 in the ML group and 55 in CT group. There were no significant differences between the groups in terms of age, sex or comorbid conditions.

Results: The incidence of intraoperative complications was similar for both groups. After surgery, nasogastric drainage was significantly (P=0·01) shorter, bowel movement and initiation of alimentation began earlier in ML group. Both groups of patients showed a significant decrease in vital capacity and forced exspiration volume postoperatively, but this depression was significantly higher (P=0·05) in CT group. The ML group also had significantly shorter stay in the intensive care unit (P=0·01) and the mean duration of the postoperative hospital stay was also significantly less (P=0·05). Generally, the patients operated by ML method during the postoperative recovery period required less analgesia, and expressed better 'overall satisfaction'. In long-term follow-up (mean: 31 months), there was no significant difference in survival rates between two groups.

Conclusions: The preliminary experiences proved that this method decreases surgical stress without endangering the safety of the patient during any point of operation and it may become the procedure of choice for selected patients with obstructive aorto-iliac disease.

inimal and direct access in thoracic diagnosis and surgery

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troduction and methods: As an alternative to Video Assisted Thoracic rgery (VATS), which uses several small openings and two dimensional leo vision, we developed the direct access technique. Here we use a 5 cm single intercostal incision to view the lung and the thoracic struc-es. The surgeon has direct three dimensional viewing and access with dified standard instruments using the Jakoscope® retractor endoscope. gh-intensity lighting from a xenon light source with fibreoptics light ides provide brilliant illumination for diagnosis and surgery. Short doscopic types of instruments, clips, and stapling devices are also used.
tient material: In the past two years we performed 119 thoracic proce-res: 57 diagnostic and 62 therapeutic operations. These include thoracic npathectomy – 21 cases, pleural or lung biopsy – 57 cases, benign medi-inal tumour – five cases, mediastinal cyst and lung cyst – eight cases, nign lung tumour – five cases, recurring pneumothorax – 23 cases.
scussion: The Jakoscope® techology provides an excellent and less pensive alternative to Video Assisted Thoracic Surgery (VATS).

It also provides excellent and 'all around viewing' of the chest cavity d structures. Palpation, suturing, and ligature placing are simple proce-res with the Jakoscope®.

It allows quick entrance into the chest and simplifies procedures espe-lly in high risk patients. The short intercostal incision is less traumatic d cosmetically better than the standard thoracic incision. It can be plied in many different types of thoracic operations. The postoperative in is reduced compared to standard thoracic operations and hospitaliza-n is shortened. We had no operative mortality. The postoperative pain d ambulation is comparable to the thoracoscopic approach.

inimal and direct access endoscopic surgery in gynecology

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e use of laparoscopic surgery for various gynecological procedures has creased during the past decade. In recent years we developed an alter-tive simpler and less expensive Minimally Invasive Direct Access rgical Technique (MIDAST^{tm}).

With this new concept and surgical technique the length of the lower dominal incision is decreased to 1/3–1/2. Minilaparotomy or mini-anenstiel incisions up to 6 cm in length or microlaparotomy incisions of m are used. The operation necessitates the use of a novel endoscopic ractor, Jakoscope® which has high-intensity illumination provided by non light source and fibreoptics wave guide. With this technology the rgeon has three dimensional-stereoscopic direct view of the operative e. It also provides direct access for palpation, suturing and cutting.

To simplify and improve precision for partial or total hysterectomy a w electrosurgical instrument GYNESNARE^{tm} was developed. It can be ed in mono or bipolar mode with the Erbotom Electrosurgical nerator. The MIDAST^{tm} has been used for the following operations in ble 1 and its advantages are shown in Table 2 and 3.

ble 1
inilaparotomy for gynecological operations:
ture of perforations of uterus
yomectomy
ysterectomy
Ovarian cystectomy
Ovarian wedge resection
Oophorectomy
Adnexectomy
Salpingectomy
Linear salpingotomy
Salpingostomatoplasty
Tubal resection and end-to-end anastomosis
Tubal sterilization
Appendectomy

Table 2
Advantages of minilaparotomy vs laparoscopy:
Shorter operative time
Extensive (commonly disposable) equipment
No CO_2 insufflation
Easy organ removing
Costs are reduced

Table 3
Advantages of minilaparotomy vs laparotomy
Shorter hospital stay
Shorter recovery period
Less pain for the patient
Cosmetic advantage
Costs are reduced

In addition, with this technique, urogynaecological operations such as Burch procedures can be performed.

Howard-Jako technique for minimally invasive direct access surgery (MIDAS) for anterior lumbar interbody spine fusion

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With the use of the Jakoscope®, a very versatile mini-lap approach to the anterior spine is now available. The Jakoscope does not have the limitations of the other retractor systems in that it can be used for all levels of the anterior lumbar spine, it supplies its own light source and does not rely on other fixation devices as K-wires or Knowles pins. Excellent direct exposure is obtained at the L4–5 and L5–S1 levels, accounting for the majority of spinal instability and degenerative disk problems of the lumbar spine. A 4–6 cm incision can be used in a transverse Pfannenstiel manor or it can be placed vertical, either in a paramedian or midline position. This approach can be used either trans-abdominally or retroperitoneally. By retroperitoneal dissection, the entire procedure can be carried out avoiding direct contact with the abdominal contents with less risk of ileus, CO_2 absorption and secondary complications from CO_2 insufflation. The Jakoscope allows for excellent direct visualization of the great vessels for ease in mobilization and management of bleeding. It is easily able to incorporate the use of the microscope or for the use of optical loupes or a micro-video camera for teaching and demonstration.

In 30 cases, the average length of stay is 2·5 days postoperative. With the exception of two vascular injuries, we have had no major complications. Minor complications of atelectasis, ileus, EUTI, etc., remain the same as, or less than those that are encountered with conventional laparotomy. The operating time for a typical inter-body fusion is under two hours, with an additional 30–40 minutes for each additional level.

We believe that the direct open mini-laparotomy approach to the lumbar spine through a 4–6 cm incision allows for a safer surgical procedure than the laparoscopic approach with an equal or shorter length of stay and a greatly reduced cost to the patient. Having performed both laparoscopic and open retroperitoneal Jakoscope approaches, we feel the Jakoscope is far superior and unlikely to be replaced with the laparoscopic procedure.

Use of a new fat pad sparing minimally invasive incision and a fibreoptic retractor (Jakoscope) in the treatment of cruciate ligament and chondral injuries

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Aim: Cruciate ligament reconstruction is common, and chondral surface replacement is being popularized. These procedures are technically demanding and problems continue to plague the surgeon. Many of these problems have to do with visualization and the pitfalls with arthroscopic approaches. In an effort to diminish these complications and reduce the operative time a Minimally Invasive Direct Access Surgical (MIDAST) approach to Cruciate Ligament Reconstruction and Chondral Transplantation has been developed.
Material and methods: Based on cadaver studies ongoing since January 1996, clinical trials with the new approach and instruments were begun in July 1997 involving 15 patients to date. By use of a randomized, controlled study, ACL, PCL and mosaicplasty have been done by the MIDAST (Minimally Invasive Direct Access Surgery) technique, arthoscopic one incision technique and by conventional Arthrotomy. Comparison in terms of anesthesia time, total incision length, need for a second surgeon, operative equipment required, and operative and postoperative complications, and postoperative morbidity were documented.
Results: The preliminary results of the three groups involving 15 patients has shown that those patients operated by the MIDAST technique had shorter operating room times and the length of hospitalization compared equally to the arthoscopic group when comparing similar procedures. Postoperative complications in each group were too few to reach any statistical significance.
Conclusions: Our preliminary conclusions are that this technique of fat-pad sparing incision and operative and postoperative complications and is equal to arthoscopic postoperative recovery. All in all, fewer instruments are needed, and the procedures are more cost effective surgery

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Leading articles

Split-liver transplantation

One of the major challenges facing organ transplanatation is the current shortage of donors. Successful outcome after liver transplantation has led to an increasing number of adults and children being assessed and transplanted. Initially, paediatric transplantation was limited by the lack of size-matched donors, particularly for children under 5 years of age, but the development of reduced-size liver transplants resolved this problem. In the technique of reduced-size liver transplantation a whole liver is reduced to left lobe or left lateral segment (LLS) and used for a small recipient, usually a child; the residual liver lobe is discarded. Liver reduction techniques led to a fall in the number of children awaiting liver transplantation, but it placed adult recipients at a disadvantage as grafts are withdrawn from the adult donor pool. This has led to increasing competition between adult and paediatric centres for the 'young' donors most appropriate for liver reduction. A further source of grafts is from living related donors; living related transplantation was introduced to transplant small children from a donor parent. However, such transplantation requires a healthy relative to undergo major surgery and it is performed most widely in countries lacking cadaveric transplant programmes. The development of split-liver transplantation (SLT)[1], in which the donor liver is divided into two grafts, LLS for a child and a right lobe for an adult, increases the number of grafts for children without affecting the adult donor pool.

The initial results of SLT were disappointing in comparison to those obtained from whole and reduced grafts, with a reported graft and patient survival of 50 and 65 per cent respectively[2–4]. Because of this, the procedure was not considered suitable for elective patients. However, collective data from Europe[5] have shown that the initial poor results were due primarily to the selection of poor-risk recipients. More recent reports have described graft and patient survival rates comparable to those achieved with whole- and reduced-size liver transplantation in good-risk recipients[6,7]. Other problems encountered in earlier cases included a high incidence of primary non-function (4–5 per cent)[4,8]. This was due to prolonged bench surgery leading to rewarming injury and prolonged cold ischaemia for the second grafts. The authors' own experience[7] is, if good-quality organs are selected, that the incidence of primary non-function or dysfunction can be reduced to a very low level even in the presence of prolonged cold ischaemia. The export of one of the grafts to another institution is developing; this relieves pressure on a hospital's resources. As results improve it should become more commonplace.

Biliary complications have long been recognized as a significant problem in SLT, affecting 5–25 per cent of recipients[3,4,8]. The increased biliary complications in the right lobe graft have been due to excessive dissection of the common bile duct during bench surgery, rendering it ischaemic. Anomalous biliary drainage may also be a cause. Biliary complications may be reduced by the use of cholangiography to identify anomalous biliary anatomy and by avoiding unnecessary dissection of the common bile duct during bench dissection. The authors prefer to divide the left duct away from the bifurcation close to the division into segment II and III ducts and the routine use of a T tube in the right lobe grafts. An increased incidence of vascular complications has been reported in SLT, with a hepatic artery thrombosis rate of 9–25 per cent, possibly due to the use of grafts with short vessels. The question of which vessels should be assigned to each graft is unresolved, with some centres keeping the main trunk of the hepatic artery and portal vein with the right graft[6,8]. We prefer to allocate the main trunk of vessels to the LLS graft, as our policy is to accept the liver for a child who receives a LLS and only to use the right lobe if splitting is anatomically feasible. Experience suggests that lengthening of the right portal vein is rarely necessary and, although the right hepatic artery may need lengthening, neither arterial nor venous thrombosis has been observed in right lobe grafts. Back-table angiography is performed routinely in some centres[6,8], but the only indication seems to be to identify whether arterial anomalies from the left gastric or superior mesenteric arteries are the sole or accessory supply to left or right grafts.

The technique of *in situ* liver splitting[5,9] has recently been described, with good short-term results from centres with previous experience of *ex vivo* SLT. The improved survival figures may be attributable to increased surgical experience of splitting livers and better patient selection. However, there are important advantages to this procedure over *ex vivo* dissection which include the avoidance of prolonged bench surgery, sharing of organs by two centres with short cold ischaemic times to both grafts, and perfect haemostasis during the donor operation leading to reduced blood loss during the recipient operation. The major drawback to the procedure is the increased operating time in the donor hospital. The transplant community has tried to minimize the inconvenience caused to donor hospitals by modifying surgical techniques to shorten donor operating time[10]. We believe that extended operations may have a potentially negative effect on other members of multiorgan retrieval teams and hospitals, thereby defeating the purpose of splitting livers. Experience has shown, if good quality organs are selected, that results comparable to *in situ* splitting can be achieved with the *ex vivo* technique.

So far 75 split-liver transplants have been performed in this centre, with a patient survival of 85 per cent at a median follow-up of 14 months. With a large paediatric programme performing approximately 55 paediatric liver transplants a year, our policy is to split any good quality organ. The index recipient is usually a child requiring elective or emergency transplantation. The LLS graft produced by SLT is similar to that of a reduced-size graft with no additional risk to the child; the right lobe is used for elective patients with chronic liver disease. Conversely, an adult patient requiring urgent transplantation would receive a whole graft and not part of a split liver. The only situation in which splitting may be performed in such unfavourable circumstances is if there are two urgent patients, one adult and one paediatric; such situations are rare.

SLT is often considered to have the potential of doubling the number of grafts available. Currently the limiting factor is the number of children suitable for LLS engraftment and this accounts for about 10 per cent of all recipients. A proportion of these will receive whole size-matched paediatric grafts. Thus the potential of SLT is only to increase the donor pool by about 5 per cent, unless the technique is developed further to permit the transplantation of two adults. Even so, the 5 per cent increase may have an impact on waiting list mortality rate. The success of SLT in our programme has reduced the need for living related transplantation. Although we have an active living related programme, within the UK only 15 such transplants have been performed, with a patient and graft survival of 93 per cent and no donor death. Our current policy is to place children being assessed for living related transplantation on the cadaveric waiting list; over the past year four children were transplanted with a split-liver graft before the assessment was completed. The waiting time for small paediatric recipients has significantly decreased.

SLT represents a significant source of paediatric liver grafts without compromising the adult donor pool, provided the right lobe graft is used in relatively stable patients. However, it remains a demanding surgical procedure that should be performed in centres with extensive experience of liver anatomy and reduced-size liver transplantation, and with resources that can cope with the extra demands placed on the institution.

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Announcement

The British Journal of Surgery, Scientific Surgery and the World Wide Web

We are pleased to announce a new initiative in this month's *British Journal of Surgery*. As part of the Journal's commitment to the practice of surgery based on scientific evidence, we will publish a page devoted to an index of randomized clinical trials in surgery. The Scientific Surgery page will appear monthly and identify all clinical randomized trials collected from 50 English language journals.

Each month the references will be added to a database on *The British Journal of Surgery* website. It is hoped this easily accessible Scientific Surgery Archive will eventually be of value to surgeons seeking sound information for the practice of clinical surgery or references for surgical papers. Details about how to access the website can be found on the Scientific Surgery page at the back of this Journal.

The Editors welcome comments and suggestions about this Scientific Surgery Initiative and about *The British Journal of Surgery* website.

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Review

Metabolic response to severe injury

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Background Severe injury is associated with a complex sequence of metabolic events. The accurate quantification of these changes and a developing understanding of their aetiology has been the product of much work by researchers over the past 60 years. An understanding of these phenomena is vital to the practising surgeon because of the plethora of new metabolic modulators threatening to become part of clinical practice.
Methods This review describes the clinical picture of the metabolic response to severe injury and then outlines modern understanding of the underlying processes.
Results and conclusion The need for further research before introduction of new technologies is emphasized.

The body's response to injury is complex, integrated, and designed to restore homeostasis and heal the wound as rapidly as possible. In the vast majority of cases this set of responses is remarkably well coordinated and quickly restores the person to health. However, in a small group of patients (those with multiple injury) the response is in excess of that required, given modern intensive care techniques; it is frankly damaging. This group of patients might benefit from metabolic manipulation, but manipulation of the host response to injury has suffered much from simplistic approaches to what has become increasingly recognized as a very complex system. This review attempts to integrate knowledge in this area in the hope that it will be useful to those caring for these patients.

Clinical picture

Ebb and flow phases of Cuthbertson

Ashen facies, a thready pulse and cold clammy extremities are the most obvious clinical manifestations of the metabolic response soon after injury. The picture changes dramatically after adequate resuscitation. The patient warms up, cardiac output increases and the surgical team relaxes. It was the Scottish biochemist David Cuthbertson who, nearly 70 years ago, first described these two distinct phases after injury[1,2]. He gave the cold clammy phase the apt title 'ebb phase' and called the warm pink phase the 'flow phase'. The distinct characteristics of these two phases are set out in *Table 1*.

Table 1 The ebb and the flow phases of Cuthbertson

Ebb phase	Flow phase
Hypometabolic	Hypermetabolic
Low core temperature	Raised core temperature
Decreased energy expenditure	Increased energy expenditure
Normal glucose production	Increased glucose production
Mild protein catabolism	Profound protein catabolism
Raised blood glucose	Raised or normal blood glucose
Raised catecholamines	Raised or normal catecholamines
Raised glucocorticoids	Raised or normal glucocorticoids
Low insulin	Raised insulin
Raised glucagon	Raised or normal glucagon
Low cardiac output	Increased cardiac output
Poor tissue perfusion	Normal tissue perfusion
Patient cold and clammy	Patient warm and pink
Preresuscitation phase	Recovery phase

Phase of haemodynamic instability

After severe injury there is usually a period of haemodynamic instability which lasts about 3 days. This is a time during which the flow phase is a staccato affair as it struggles to break from the grip of the ebb phase. The patient requires both colloids and inotropes in addition to crystalloids over this period but, once the flow phase has fully developed, colloid infusion and increasing inotropic support are no longer needed. A recent study in this department of ten critically injured patients (median Injury Severity Score of 35) found a positive fluid balance of about 4·7 litres on average over this period and in most of the patients clinical oedema was obvious[3].

Hypermetabolic or flow phase

The swollen patient, now stable and well perfused, enters the flow phase during which profound metabolic interchanges occur. The patient is weaned from the respirator and, with inotropes withdrawn, leaves the intensive care unit for the ward. Diuresis occurs and the body-weight falls steadily (approximately 0·6 kg/day), pretrauma weight being reached around the end of the second week. If all goes well discharge home may be expected 4–7 weeks later. Now, especially if suffering the after-effects of head and skeletal injury, although wasted, weak and lacking volition, the family will note substantial improvements as each week progresses.

Metabolic picture

All illness results in oxidation of body protein and fat, and an increased hydration of the fat-free body mass. Such changes have recently been quantified in a group of

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critically injured patients within the context of modern trauma care[3]. Nearly one-fifth of the body's store of protein is lost over the first 3 weeks, most during the first 10 days. Two-thirds of the loss is from skeletal muscle. It is this loss of skeletal muscle protein which leads to problems with respiratory function and subsequent weaning from ventilators, and it is one of the major factors influencing morbidity and mortality following injury[4]. If adequate energy intake is administered fat is not burned as fuel and body fat stores are not diminished. The study also showed that the 5 litres or so of resuscitation fluids retained early on are mainly located in the extracellular space. As recovery progresses this excess extracellular fluid is excreted. Although intracellular fluid also steadily decreases over time this decrease is broadly in proportion to the loss of other cellular constituents.

Hypermetabolism

All injured patients have a rise in resting energy expenditure of 5–60 per cent depending on the magnitude of injury. In the multiply injured patients described above there was an increasing energy expenditure, maximal at about 10 days after injury, as the flow phase developed. This increased energy expenditure signifies increased oxygen consumption by the body to support the massive exchanges of substrate between organs that occur as a part of the metabolic response.

Altered protein metabolism

The loss of protein from the body after injury was first recognized more than 60 years ago. Cuthbertson in 1932[1] described a group of patients who had sustained orthopaedic trauma, and noted an enhanced loss of nitrogen (16 per cent of protein is nitrogen) from the body. This negative nitrogen balance was maximal from day 2 to day 8 after the injury and lasted for up to 1 month. Cuthbertson concluded that the increased nitrogen came from breakdown of skeletal muscle protein, suggesting that it was 'to meet the exigencies of the metabolism of the recuperative process'[2]. This concept was later developed by Moore: 'it is our conviction that the destruction of lean tissue mass has as its purpose the provision of raw materials for wound healing'[2,5].

In prolonged critical illness the initial response is the breakdown of liver and muscle glycogen stores. Following rapid exhaustion of glycogen, new glucose is derived from gluconeogenic precursors which arise primarily from skeletal muscle protein. This is accompanied by a blunting of the normal adaptive ketoaemic response to starvation[6]. Important products of this protein breakdown in skeletal muscle are the amino acids alanine and glutamine. Glutamine is the most abundant free amino acid in the body, and its intracellular concentration falls profoundly after trauma and may remain low for many weeks[7]. Glutamine's importance lies in the fact that it is a prime fuel for the enterocyte and the cells of the immune system; it is thus important for gut barrier function and immunity[8,9]. While there is an increase in protein catabolism in critical illness there is a corresponding, but lesser, increase in protein anabolism[10]. The net result, however, is catabolic.

Altered fuel metabolism

Fat constitutes the major fuel reserve of the body. The critically ill patient has a high turnover rate of free fatty acid (FFA) and glycerol, which is suppressed during glucose infusion. Re-esterification of FFA occurs at an accelerated rate and FFA oxidation is increased, leading to the conclusion that fat is a major fuel in the traumatized patient[10], but this applies only if nutritional support containing adequate energy intake has not been given[3].

Glucose is the principal fuel supplying the relatively hypoxic injured tissues and the cells within them. Lactate is produced and released into the circulation for transport back to the liver for the further production of glucose (Cori cycle). Most of the new glucose is produced by the liver not only from lactate but also from alanine and other glucogenic amino acids. Although this endogenous glucose production can be suppressed in the normal subject by the infusion of glucose, in the injured patient this occurs to a limited extent only[10].

Altered water metabolism

Forty-five years ago Dr Francis Moore of Harvard Medical School, using isotopic dilution studies, described changes in water metabolism in injury[5]. Body water changes closely parallel body-weight changes and are largely accounted for by changes in extracellular water[3]. In younger patients this excess is excreted readily but older patients take twice as long to excrete this fluid[11]. This may contribute to a poorer outcome in the elderly from critical illness.

Initiators and propagators of the metabolic response

Traditionally the metabolic response to injury has been viewed as a neuroendocrine reflex arc, with pain and hypovolaemia stimulating the brain to coordinate a massive outpouring of counter-regulatory hormones which produce glycogenolysis, fat catabolism and protein breakdown. Recently this view has been challenged with the discovery of a huge array of mediators and with developing research into the recovery or flow phase of injury.

Role of the neuroendocrine response

Campbell and associates[12] and Ingle *et al.*[13] in the late 1940s and early 1950s investigated the role of glucocorticoids in protein metabolism, demonstrating that in adrenalectomized rats the loss of nitrogen observed following femoral shaft fracture in control rats is obliterated. Egdahl[14] demonstrated convincingly the importance of the peripheral nervous system in the early endocrine response to injury. He disconnected a limb from the body of an anaesthetized dog, leaving only the sciatic nerve and femoral artery and vein. Trauma to the enervated portion of this limb evoked glucocorticoid secretion. The nerve was then divided and repeated trauma failed to produce a rise in glucocorticoids. Infusion of the counter-regulatory hormones (catecholamines, glucocorticoids and glucagon as a triple hormone infusion) into normal human volunteers, in concentrations seen in the ebb phase, results in metabolic alterations qualitatively similar to those observed in injured patients[15]. Importantly, however, the nitrogen loss noted with this combination of hormones is modest and not associated with net skeletal muscle protein breakdown.

Bessey and Lowe[16] showed that by using somatostatin to block insulin secretion, as observed in the ebb phase of injury, a triple hormone infusion results in much larger nitrogen losses. They also showed that excessive nitrogen loss in the first 48 h of an insulin suppressive triple hormone infusion, compared with a standard triple hormone infusion, is not associated with increases in forearm amino acid nitrogen efflux (the forearm being used because its predominant metabolically active tissue is skeletal muscle). This suggests that the nitrogen originates elsewhere, probably from splanchnic tissues as the gut has one of the highest protein turnover rates in the body. Catecholamines appear to be important for altered fat metabolism. The increased rates of lipolysis and triglyceride turnover observed in the injured patient are probably due to increased catecholamine activity, β-activity promoting lipolysis and α-activity leading to inhibition of FFA turnover[17].

Extension of the neuroendocrine response into the recovery phase may lead to a prolonged convalescence. Elderly patients, who appear to have a normal metabolic response to injury often suffer from this[18,19]; after hip fracture they have a prolonged increase in plasma cortisol which may partly account for an extended loss of body protein and poor recovery[19].

Role of cytokines

Significant objections to the role of the neuroendocrine axis as the sole mediator of the metabolic derangement after injury were previously voiced by Cuthbertson. He noted that the neuroendocrine response to surgery was limited to 24 h, whereas the increased nitrogen output attained its maximum several days later during the recovery phase[20].

In addition to efferent nervous signals, circulating factors also initiate the metabolic response to injury. Drucker *et al.*[21] studied paraplegic patients with chronic decubitus ulcers, noting that an operation on a denervated area results in alterations in glucose metabolism. Wilmore *et al.*[23] later showed that patients with burn injury and spinal transection maintain a hypermetabolic response, as do similar patients in whom the afferent nervous signals are interrupted by local, regional or general anaesthesia. They also showed that only in patients with brain death was the hypermetabolic response to burn injury diminished. In 1893 Coley[23] demonstrated the regression of tumours injected with bacterial toxins. The cause and significance of this phenomenon remained obscure until 1985 when Cerami's group purified the cytokine tumour necrosis factor (TNF)/cachectin[24,25]. Independent work by others led to purification of interleukin (IL) 1, a key mediator of the hepatic acute-phase response and an endogenous pyrogen.

TNF infused into humans and animals induced a net catabolic state by mediating increased catabolism at the level of specific tissues, by causing anorexia, and by activating the hypothalamic–pituitary–adrenal axis[26–29]. The metabolic effects after TNF administration are dose related and with increasing dose include enhanced energy expenditure, increased hepatic gluconeogenesis, increased whole body protein breakdown, activation of the hypothalamic–pituitary–adrenal axis and increased whole body lipolysis; these are all features of the metabolic response to injury. In even larger doses TNF triggers potentially catastrophic tissue injury and lethal shock[30,31].

Like TNF, IL-1 in lower concentrations is beneficial; it stimulates defence mechanisms[32]. However, in higher concentrations, it stimulates the production of a number of mediators which cause other biological effects, including fever, hypotension, inflammation and proteolysis, possibly via the lysosomal energy–ubiquitin-dependent proteolytic pathway[33–36].

IL-1 and TNF may have a synergistic effect in producing the metabolic manifestations seen after injury or infection, as infusing the two cytokines together in rabbits has more effect than either of the cytokines alone on energy substrate metabolism[37]. However, three pieces of evidence argue against systemic cytokine release accounting for all of the metabolic changes seen after injury. First, cytokines have not been consistently found in the bloodstream of injured patients (with the exception of IL-6). Second, the effects of intravenously administered cytokines, although profound in the short term, are not sustained and tend to diminish quickly. Third, cytokines do not appear to have direct effects on muscle protein breakdown.

Attention therefore has recently turned to the role of cytokines at the tissue level, such as the liver and the central nervous system. IL-1 and IL-6 have been detected in the cerebrospinal fluid of head-injured patients, and IL-1 may be able to cross the blood–brain barrier[38–40]. TNF receptors are present in murine brain and TNF is produced by rat astrocytes *in vitro*[41,42]. TNF and IL-1 are found in the cerebrospinal fluid of children with meningitis and in experimental meningitis, TNF is found in the cerebrospinal fluid but not in the serum, suggesting that it can be produced by the brain[43–46]. There is also an extensive network of IL-1 nerve fibres enervating the hypothalamus and recent work has demonstrated that chronic central nervous system exposure to IL-1 produces catabolism in the rat that is not mediated by glucocorticoids[47]. After thermal injury a very early rise in liver and lung IL-1 is observed[48] and infusions of IL-1 by differing routes produce different effects[34], suggesting that IL-1 is produced in, and acts on, different organs to produce many of the responses seen after injury[49].

The role of IL-6, which may be an important mediator in the ebb phase, is probably to stimulate the liver to produce acute-phase proteins. This may account for some of the nitrogen loss which occurs in severe injury[50]. Although very high levels of IL-6 correlate with death after trauma, IL-6 may only be a marker of severity of injury (like C-reactive protein) rather than a major causal agent[51,52].

Although the relative contributions of cytokines and counter-regulatory hormones are unclear, they appear to have synergistic effects. When IL-1 is induced by etiocholanolone injection and counter-regulatory hormones are infused simultaneously, there is a substantial increase in protein breakdown compared with either stimulus given alone[53]. The roles of IL-1 receptor antagonists, soluble IL-1 and TNF receptors remain to be clarified, although it seems likely that they act to prevent the deleterious effects of unchecked production of TNF and IL-1[49].

Role of the wound

The site of injury probably also plays an important role. Neutrophils and macrophages are attracted to the site and, in addition to producing cytokines, they generate important mediators which act locally on the wound and distally on organs such as the liver, gut and skeletal muscle. These mediators include platelet activating factor, oxygen free radicals, nitric oxide and arachidonic acid metabolites. They act both directly on cells and indirectly by altering regional blood flow[54–57]. The complement cascade is also involved as complement is activated after injury[58,59] and is able to stimulate monocytes to produce IL-1[60,61]. At present the role of the wound is uncertain but what is clear is that the wound releases a large number of mediators with the potential for metabolic activity. Whether or not they act in any more than a paracrine fashion remains to be shown.

Role of cellular dehydration

According to Haussinger *et al.*[62], the profound loss of body protein that occurs in injured patients is triggered and maintained by cell shrinkage secondary to cellular dehydration. Finn and the Auckland group[63] measured the total body content of protein, potassium and water and its compartments in nine patients with blunt multiple trauma. They found that cells lose water in quantities greater than would be expected from protein losses. Haussinger's work was mainly with isolated cells and these new clinical data support the hypothesis that cellular dehydration is a trigger for protein catabolism. It has, however, been argued by some that the relationship between cellular dehydration and proteolysis is not so clear cut, and that cell shrinkage is merely an epiphenomenon. Concomitant with these changes in cellular hydration are changes in cellular energetics[64].

Role of the gut

The gut has been considered 'the motor of multiple organ failure'. This concept has been supported by a number of animal (but only a few human) studies, demonstrating translocation of bacterial products across the gastrointesinal tract after shock and other injuries[65]. Severe injury is thought to lead to increased intestinal permeability which is related to a systemic inflammatory response[66,67]. In this model, changes in intestinal flora, coupled with impairment of the normal barrier function of the gastrointestinal tract, allow the bowel to serve as a reservoir of pathogens. From this reservoir they or their products may enter the portal and systemic circulations, thereby fuelling the ongoing metabolic process either directly or via activation of macrophages to produce cytokines in either the liver or the mesenteric nodes[68,69]. The alteration in gut permeability is probably related to glutamine deficiency in stress states. Glutamine is an important fuel for enterocytes and in the presence of glutamine deficiency the gut mucosa atrophies and a breakdown of gut-barrier function occurs[70].

Although there is a plethora of animal data supporting this hypothesis it has remained difficult to demonstrate after human injury[71]. In addition, much of the work in humans has been done in the ebb phase of injury, which is unlikely to be the ideal time for such a study. Because of this, a role for bacterial translocation in the pathogenesis of the metabolic response to severe injury cannot be entirely discounted, but further work is needed.

Role of ischaemia–reperfusion

The role of the ebb phase is probably to set the stage for the more profound metabolic alterations of the recovery phase. The ebb phase acts as an ischaemia–reperfusion event, especially for the gut. Reductions in regional intestinal blood flow result from stimuli such as hypovolaemia, acidaemia and hypercarbia, via hormonally and neurally mediated splanchnic vasoconstriction[72]. With resuscitation there is secretion of the counter-regulatory hormones, a decrease in insulin and the generation of

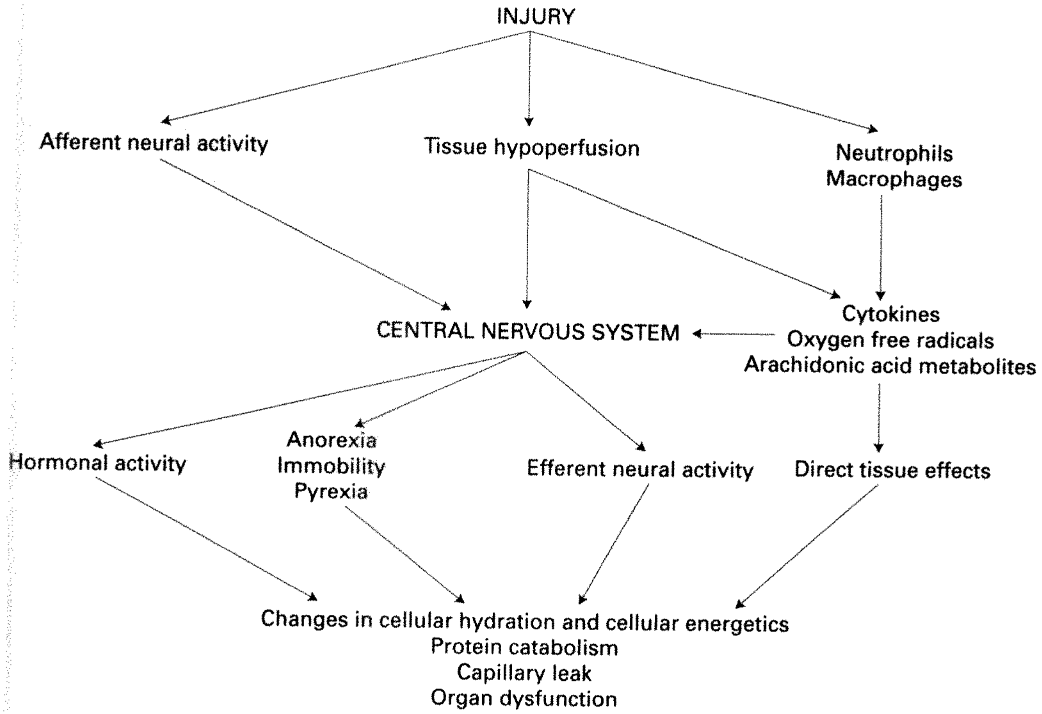

Fig. 1 Injury produces afferent neural activity, hypoperfusion and immune activation. These, in turn, set up a cascade of events coordinated by the central nervous system and at the level of individual tissues such as the liver, gut and skeletal muscle. These events are mediated by a complex array of neutrophil and macrophage products. The end results are changes in cellular energetics and hydration, lysis of skeletal muscle and visceral protein, capillary leakage into the lungs and subcutaneous tissues, and organ dysfunction

mediators, such as oxygen free radicals, eicosanoids, complement, nitric oxide and cytokines (TNF, IL-1, IL-6, IL-8), and the activation of neutrophils. With the restoration of tissue perfusion, especially in extreme injury involving contaminated and damaged tissue, these mediators, in association with anorexia, pyrexia, and immobility, act to cause the skeletal muscle protein breakdown characteristic of the flow phase. This protein breakdown is critical in slowing recovery from injury.

Role of immobility

Bedrest leads to a catabolic state characterized by muscle weakness, muscular atrophy and a negative nitrogen balance[73]. The protein loss, however, is only a fraction of that observed in severe injury; it is probably due to decreased whole body protein synthesis as protein breakdown is not a feature[74,75]. Glucagon and cortisol levels are raised, which may explain the insulin resistance noted in this situation, but there are no changes in catecholamines or growth hormone[76].

Future avenues for metabolic response modification

The metabolic response to injury is not a simple system. Further work is needed on the compartmentalization of cytokines and other signal proteins[49]. The critical role of the central nervous system needs to be elucidated. The roles of the gut and the wound itself remain unclear and further investigation is required in these areas in the human.

Conclusion

The response to injury may conveniently be divided into an ebb (resuscitative) phase and a flow (recovery) phase. The metabolic perturbations of the resuscitative phase are best understood as a reflex arc of the peripheral nervous system and the immune system, using cytokines as the afferent limb, the central nervous system as the co-ordinator, and the counter-regulatory hormones as the efferent effectors. These effectors, along with alterations in tissue oxygenation, free radical generation, cytokine production and other mediators, set the stage for the profound metabolic changes of the recovery phase (*Fig. 1*). Cytokines are produced in injured states which are capable of stimulating neuroendocrine activity, hepatic acute-phase protein production, anorexia, fever and net protein catabolism; these are all features of the metabolic response to injury. It is likely that they are key players in this response and that their effect is mediated via the hypothalamus. Also important are efferent central nervous system activity, immobility, oxygen free radicals, arachidonic acid metabolites, the complement cascade and altered gut permeability following the ischaemia–reperfusion insult of injury.

Therapeutic intervention with anticytokines, epidural anaesthesia, growth hormone and nutritional modification has shown some promise in arresting the massive losses of protein observed after severe injury, and has led to better understanding of the underlying mechanisms involved. However, much work is required to find the correct combinations for use in individual patients. Much effort is also required to achieve a better understanding of the complex alterations in body chemistry that occur after injury. Understanding these phenomena may lead to a future in which critically ill patients will be treated with specific therapies directed at conservation of body protein and healing of the injury.

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Review

Diet, reflux and the development of squamous cell carcinoma of the oesophagus in Africa

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Background Squamous cancer of the oesophagus has reached epidemic proportions in Africa in the past few decades. There are many known associations but as yet no well established theory of causation.

Methods Relevant literature was found by manual review of appropriate journals and literature, Medline searches and cross-referencing. Published theories of causation of endemic cancer of the oesophagus were assessed in the light of available evidence. A hypothesis based on that evidence was formulated.

Results and conclusion A predominantly maize-based diet is high in linoleic acid, a precursor for gastric prostaglandin synthesis. In combination with low intake of other fatty acids and riboflavin, high levels of prostaglandin E_2 are produced in gastric mucosa, leading to reduced gastric acid secretion, relaxation of the pylorus and a reduction in lower oesophageal sphincter pressure. These events result in combined reflux of duodenal and gastric juices low in acidity into the oesophagus. Resulting dysplasia strongly predisposes to local squamous carcinogenesis. This is now a fertile area for research, which may open the way for preventive action.

Squamous cell cancer (SCC) of the oesophagus is a major cause of death worldwide. It is particularly common in the Linxian region of China, the Caspian littoral region, Iran and Southern Africa, and has been described in these areas as endemic. A wide variety of factors have shown an association with endemic SCC. Common factors include a diet based on either maize or wheat, a poverty of minerals and vitamins in the diet, and little fresh fruit and vegetable consumption[1]. Tobacco use has a clear association in Africa[2–4]. Some specific local carcinogens have been postulated such as alcoholic concoctions in South Africa[5] and opium in Iran[6]. However, these have not had a causal link proven and ongoing search for the predominant carcinogen in each region has thrown up many possible but no probable candidates.

Postulated causal mechanisms

Postulated causal mechanisms for endemic areas include those involving direct insult or local carcinogenesis by a single agent and multifactorial hypotheses including (1) direct insult plus carcinogen, (2) direct insult plus carcinogen and nutritional deficiency, and (3) carcinogen plus nutritional deficiency.

Single agents

Direct insult. Maize-based beer and alcohol in general have been proposed as major factors in South Africa[7,8]. There is no consistent association, however, between alcohol and SCC in endemic areas[2,4]. A significant proportion of patients with SCC in endemic areas do not consume alcohol[2,3].

Carcinogen. Tobacco carcinogenesis is widely advocated as an adequate single cause. The evidence that tobacco is a carcinogen involved in endemic SCC aetiology is overwhelming[2,3]. As with alcohol, many patients with SCC do not use tobacco at all[2,3], ruling out tobacco as the single cause of high incidence.

Fungal mycotoxins[9] and viral infection[10,11] both have associations with SCC, and have been put forward as carcinogenic agents, but the evidence remains circumstantial.

An unidentified carcinogen in the full Transkei diet was postulated by Purchase *et al.*[12], based on experimental studies in rats. A higher incidence of cancer of the oesophagus was evident on a full Transkei diet compared with a restricted diet. Particular suspicion was cast on wild vegetables including *Solanum nigrum* (garden nightshade). Nitrosamines in food have also been suggested but, again, the evidence is circumstantial[13].

Multifactorial mechanisms

Direct insult plus carcinogen. Tobacco plus alcohol is a well documented causal combination[14–16]. Alcohol may act as an oesophageal irritant, a solvent for the carcinogens of tobacco, or as a true co-carcinogen. Van Rensburg[1] and Wynder and Stellman[17] believe its effect is to cause or accentuate dietary deficiencies of minerals and vitamins. The combination of tobacco and alcohol is well established in non-endemic areas as the major causal association of SCC, although not in endemic areas.

Direct insult plus carcinogen plus nutritional deficiency. Several studies support this hypothesis. Warwick and Harington[18] reviewed the evidence in Transkei and suggested that a combination of local

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alkalinization from tobacco use, combined with nutritional deficiency (particularly pellagra) and other physical insults (including excess alcohol and plant emetics), are responsible for SCC, with or without the effects of carcinogens in local tobacco. Bradshaw and Schonland[19] cite oesophageal insults, including smoking, alcohol and emetics, combined with a general state of malnutrition and an unidentified carcinogen.

Morris and Price[20] hypothesized that papillomavirus was an essential part of the carcinogenic process, causing a 'glycogenic acanthosis', a process favoured by a reduction in immune competence in malnutrition. Smoking, alcohol, aflatoxins and malnutrition would all contribute to successive stages in the progression to dysplasia and carcinoma.

Carcinogen plus nutritional deficiency. Van Rensburg[1,2,21] has argued consistently that the staple diets of all endemic areas are deficient in a range of micronutrients, particularly zinc, magnesium, riboflavin and nicotinic acid, predisposing to carcinogenesis by agents as yet not clearly identified.

The concept that dietary deficiency is the major problem has been challenged by the finding that SCC is a disease of people of some education and means[2]. A case–control study in Transkei[3] found no association with a history of pellagra, the main deficiency disease associated with a maize diet. In Africa, cancer of the oesophagus is nevertheless closely associated with the use of maize as a staple dietary element. The deficiencies of such a diet have been studied repeatedly, but the effects of the constituents of maize have been spared close examination.

A two-stage hypothesis of carcinogenesis is consistent with the available data: (1) predisposition by a diet-associated low-acidity duodenogastro-oesophageal reflux (DGOR) and (2) carcinogenesis by a variety of agents.

Steps of a new hypothesis

1. A high level of linoleic acid ingestion is associated with increased prostaglandin E_2 production in the stomach. Other dietary factors increase this effect (Fig. 1)

SCC has followed some decades after the adoption of maize as the dietary staple in east Africa, mirroring its geographical spread. Throughout the world, all areas of high risk for SCC use maize and/or wheat as staples[1]. The risk rises with increasing consumption of maize by the individual[2,22]. Van Rensburg[1] described the association in Africa as fitting with 'prolonged exposure to a predominantly corn diet dating from childhood'. Maize is rich in linoleic acid and very low in other essential fatty acids. A case–control study in Natal showed that the more frequently bought maize meal is consumed, the higher the risk of cancer of the oesophagus[2]. The relative risk of daily as against weekly buying of maize meal was 5·7 : 1. In the community studied, three maize forms are consumed, whole kernels, stamped (broken) maize and maize meal. Whole kernels are poorly and slowly digested, releasing little oil in the stomach. Stamped maize has the oil-containing husk removed and provides no linoleic acid at all. Maize meal is the preparation which provides all its linoleic acid to the stomach in an easily digestible form. A similar significant association with the consumption of maize meal was found in a high-incidence area of Italy[22].

Linoleic acid is a prostaglandin precursor. Wistar rats fed a long-term diet high in linoleic acid develop a sustained increase in prostaglandin (PG) E_2 levels in the stomach[23]. PGE_2 production is promoted by absence in the diet of other fatty acids[24] which cause competitive inhibition. In African endemic areas for SCC, there may be little dietary fat apart from that in maize; dietary fat from sources other than maize is negatively associated with SCC[2,3].

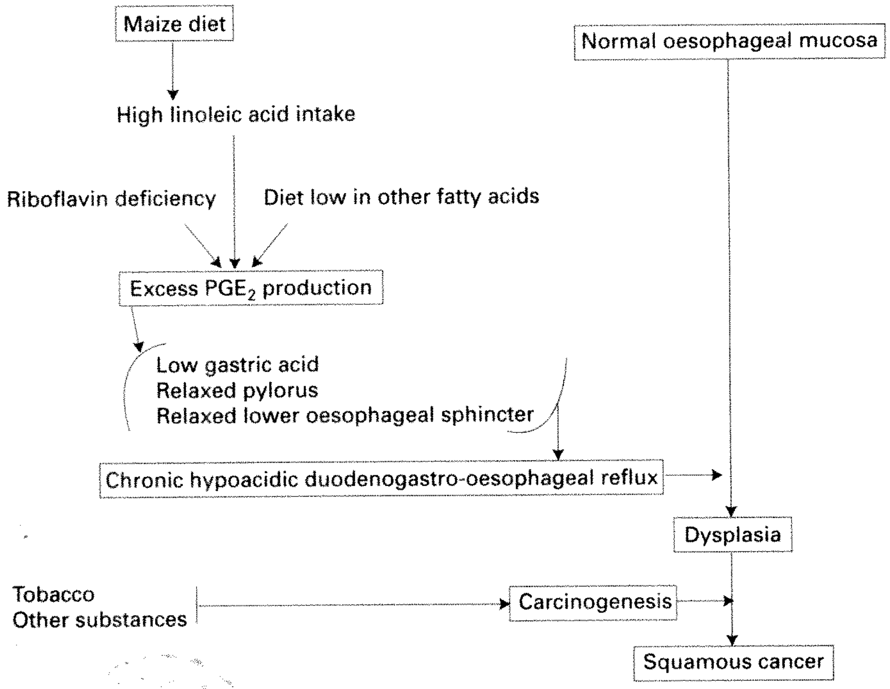
Maize diet
Normal oesophageal mucosa
High linoleic acid intake
Riboflavin deficiency
Diet low in other fatty acids
Excess PGE2 production
Low gastric acid
Relaxed pylorus
Relaxed lower oesophageal sphincter
Chronic hypoacidic duodenogastro-oesophageal reflux
Dysplasia
Tobacco
Other substances
Carcinogenesis
Squamous cancer

Fig. 1 A diet based on maize with deficiency of other elements will lead to high prostaglandin (PG) E_2 production and a chronic low-acid oesophageal reflux, with consequent predisposition to cancer

Riboflavin deficiency results in an increased biosynthesis of PGE_2[25] through a deficiency of glutathione peroxidase, which is dependent on the sulfhydryl group provided by riboflavin. Riboflavin deficiency is a factor common to the major endemic areas of the world for SCC[26,27]. Maize diets contain inadequate riboflavin and riboflavin content is further reduced by any refinement[1]. Riboflavin deficiency has been implicated in the early stages of oesophageal cell proliferation and dysplasia[28].

The scenario in which a high level of PGE_2 will be produced is a diet rich in linoleic acid, low in other fatty acids and deficient in riboflavin. A diet heavily dependent on maize creates exactly this combination and will promote a high level of gastric PGE_2 production.

2. PGE_2 inhibits gastric acid secretion and reduces the tone of the pyloric and lower oesophageal sphincters, resulting in a chronic hypochlorhydric DGOR

PGE_2 causes a reduction in lower oesophageal[29] and pyloric sphincter pressures[30,31], with a reduction in both basal and stimulated gastric acid output[23]. The logical result is increased oesophageal reflux of gastroduodenal fluid of reduced acidity. Heartburn is very common in Transkei, affecting 60 per cent of a group of healthy people studied. Symptomatic regurgitation of fluid identified as bile was present in 75 per cent of sufferers. Heartburn can be abolished by aspirin[32].

3. Chronic low-acidity DGOR predisposes to squamous carcinogenesis

With reduced concentrations of gastric acid, any refluxate into the oesophagus has a higher pH than normal. This predisposes to the development of carcinoma. Seto *et al.*[33] subjected three groups of rats to oesophageal carcinogens: gastrectomized rats with regurgitation of duodenal contents, gastrectomized rats without regurgitation, and healthy controls. All the animals in the group with duodenal regurgitation developed cancers which were exclusively squamous; none of the other groups developed any cancers. Oesophagitis and severe dysplasia were present in association with the cancer-bearing areas.

Partial gastrectomy is a known risk factor for delayed (15–20 years) squamous cancer of the oesophagus. About 8 per cent of patients with squamous cancer of the oesophagus will have had a previous gastrectomy[34], the risk increasing with time since gastrectomy. Lower oesophageal sphincter function is often impaired[35] and acid production is reduced or abolished after major gastric resection. Colin-Jones *et al.*[36] reported a relative risk of 2·3 for cancer of the oesophagus at 5–7 years after cimetidine use, but did not state whether this was predominantly SCC or adenocarcinoma. Enteral PGE_2 has been shown to promote oesophageal carcinogenesis in rats[37].

A possible mechanism for the carcinogenic effect of a chronic hypoacidic DGOR is shown in *Fig. 2*. Epidermal growth factor (EGF) and transforming growth factor (TGF) α are products of salivary glands, oesophageal mucosa and stomach. Luminal overexpression as well as high binding activity have been implicated in proliferative drive and carcinogenesis in the gastrointestinal tract[38–41] and elsewhere[42,43]. Growth factors are partially or wholly inactivated by trypsin[44] and by pepsin if the pH is below 4[45]. Interference with normal activity of these two proteases will allow growth factors to be more active (longer or at higher levels) in the oesophagus. A reflux of duodenogastric juice at a pH of 4 or above will contain no active pepsin, but will contain active EGF and TGF-α, and will not inactivate salivary growth factors.

It is of great interest that constituents of staple diets of east and southern Africa include beans and pumpkin, which contain trypsin inhibitors[46,47]. *Solanum nigrum*, which is used as a vegetable in some parts of Africa[48], contains a pepsin inhibitor[49] and has a significant association with SCC in Transkei[3]. Oesophagitis and squamous dysplasia are strongly associated with endemic SCC in Africa and beyond[50,51]. Oesophagitis has been

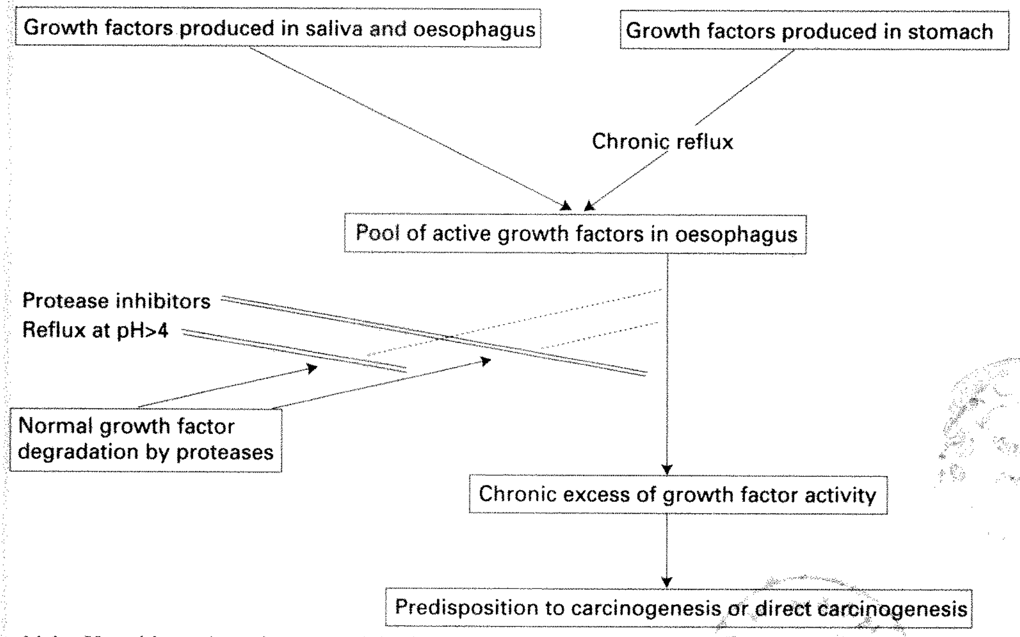
Growth factors produced in saliva and oesophagus
Growth factors produced in stomach
Chronic reflux
Pool of active growth factors in oesophagus
Protease inhibitors
Reflux at pH>4
Normal growth factor degradation by proteases
Chronic excess of growth factor activity
Predisposition to carcinogenesis or direct carcinogenesis

Fig. 2 Reflux of a high pH and ingestion of protease inhibitors ensure excess growth factor activity in the oesophagus

proposed as a precursor lesion[50], but more recent evidence suggests that the true precursor lesion is the concomitant dysplasia, with significant risk only from moderate dysplastic change[52].

Tobacco has a known association with SCC in Africa, and its use brings with it a relative risk of up to 5·99 compared with non-smokers[2,3]. It has been noted, however, that other racial groups in South Africa use much more tobacco than Africans, yet have a markedly lower incidence of oesophageal cancer, implying that other factors must be important. The oesophagus may be predisposed to carcinogenesis from a variety of sources.

Discussion

Any theory of causation needs to explain the consistently reported associations of endemic SCC of the oesophagus with (1) heavy dependence on a maize-based diet over a very long term, (2) slow rise in incidence, (3) relative poverty and (4) tobacco, at a high-risk level.

The rise of SCC has followed decades after the introduction of maize. It takes a considerable time to supplant another staple or group of staples and for maize to become almost the only constituent of the diet, then finally for maize meal to become the predominant form ingested. The finding that SCC is a disease of people of some education and means[2] can be accounted for by poorer people eating more stamped maize and kernels, and the richer, transitional group eating more maize meal.

Tobacco has a well proven record of association with a high relative risk. It seems to be a more potent carcinogen in the endemic situation than in non-endemic populations. Studies from endemic areas have, however, shown a significant percentage of non-smokers among victims of SCC[2,3]. This implies that tobacco is working synergistically or on a predisposed mucosa; it may be only one of a number of carcinogens to which the oesophagus is exposed. In addition, cigarette smoking encourages gastro-oesophageal reflux[53].

The association of SCC with alcohol, which has been well demonstrated in non-endemic areas, has never been established in endemic areas. Low-dose alcohol stimulates acid secretion[54] and also causes gastro-oesophageal reflux[55]. It is possible that alcohol has no additive effect to the factors already operating to cause a low-acid reflux. The dominance of squamous cancer fits in well with the finding that acid reflux favours columnar differentiation/regeneration[56–59]. The process of differentiation is affected by growth factors[60–62] and the local oesophageal environment of low-acid reflux may affect this activity.

The steps of a hypothesis have been described, with supporting evidence linking these elements to endemic areas in Africa. While the steps have been based on the African situation, there are many features common to other endemic areas, which share some of the pathways described. The major implication of this hypothesis is that preventive measures are possible, even in medically underserved areas which suffer the endemic form of this disease.

A further issue raised is that a chronic low-acid reflux may increase squamous carcinogenesis. The increasing availability of acid- and pepsin-suppressive therapies, which can create a hypochlorhydric gastro-oesophageal refluxate low in protease, could increase the risk of squamous carcinogenesis with long-term usage, particularly in African populations.

In the Western world, the possible links between diet, tobacco and chronic drug therapies deserve wider attention. This is particularly so in the light of dramatic rises in the incidence of adenocarcinoma and its known association with Barrett's metaplasia as a consequence of chronic gastro-oesophageal reflux[63–65]. It is intriguing that duodenogastric reflux may also play a part in the development of Barrett's metaplasia, adding a further similarity between SCC and adenocarcinoma aetiologies. This is also worthy of careful dietary study.

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Review

Metachronous colorectal cancers

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Background Up to 9 per cent of patients who undergo resection for colorectal cancer develop metachronous cancers. There is no consensus on the detection and management of such cancers.

Methods The literature was reviewed exhaustively regarding the incidence, clinical characteristics, detection, treatment and molecular genetics of metachronous colorectal cancers. This was based on a Medline search from 1966 to December 1997 for articles on metachronous colorectal cancers. A manual search was also performed on references quoted in these articles. All publications relevant to this study were included.

Results Although the underlying causes for metachronous colorectal cancers are yet to be elucidated, risk factors for the disease have been identified. These include the presence of synchronous polyps or cancers, a history of metachronous cancers, and hereditary non-polyposis colorectal cancer (HNPCC).

Conclusion Preoperative colonoscopy and postoperative colonoscopic surveillance are essential in identifying patients at risk of metachronous colorectal cancer. A total colectomy and ileorectal anastomosis should be considered for some patients, certainly for those with HNPCC.

Definition

A primary large bowel cancer which occurs at any time after the surgical achievement of a 'clean' colorectum (i.e. free of all neoplasms) is termed metachronous[1–4]. The malignancy must be unequivocally new and not a recurrence or metastatic deposit of the initial lesion[5].

There is little consensus regarding the distinction between truly metachronous and missed synchronous large bowel cancers. Neoplasms occurring after a set interval from the index cancer are described as 'metachronous' while those discovered before this time are termed 'missed synchronous'. Studies have used various intervals (6 months[4,6–8], 1 year[9,10], 2 years[11–15] and 3 years[16,17]) from the initial cancer to differentiate the two conditions.

It is essential that synchronous cancers and polyps are identified before surgery. Universal colonoscopy is the optimal method but logistic, financial and manpower implications limit its routine use. A selective policy is therefore more practical[18]. In 35 per cent of patients the index cancer may not admit the colonoscope; peroperative colonoscopy should be considered[16] or a clean colon established within 3–6 months of surgery[11,19].

Incidence

A lifelong risk of developing metachronous colorectal cancer exists in all patients who have undergone large bowel resection for malignancy[2,11,15,20]. The risk is believed to have a small but definite increase with length of survival after the first operation for colorectal cancer[1]. The incidence of metachronous colorectal cancer is estimated at 0·6–9 per cent[11,12,21–23]. This variation in incidence is a reflection of the fact that the number of new large bowel primaries detected is directly proportional to the length of follow-up[11,15]. The annual rise in incidence with length of survival following index surgery is estimated at 0·35 per cent per annum[15]. The cumulative incidence rises to 30 per cent after 41 years of follow-up[11].

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Evolution of metachronous colorectal cancers

The time it takes a metachronous colorectal cancer to develop after surgery for the index tumour varies widely. Some authors estimate that between 20 and 46 per cent of metachronous colorectal cancers are diagnosed within 2 years of the primary operation[1,14]. Agrez *et al.*[4] reported that 50 per cent of metachronous cancers occur within 5·5 years, a finding confirmed by Kaibara *et al.*[9]. A varying average interval to detection of metachronous colorectal cancer is reported in the literature: 3·5 years[13], 7 years[15], 11 years[7], 12 years[24] and as late as 41 years into follow-up[11].

Although the adenoma to carcinoma sequence is thought to take about 5–15 years[25,26], it is not known whether this applies to the development of metachronous colorectal cancer. Metachronous and synchronous tumours are features of hereditary non-polyposis colorectal cancer (HNPCC) syndrome which is characterized by a genetic predisposition to colorectal cancer (usually on the right side) at an early age, and extracolonic malignancies of the endometrium, ovary, stomach, small intestine, biliary tract, ureter, renal pelvis and pancreas[27,28]. Jass *et al.*[29] believe that adenomas in patients with HNPCC are more likely to be villous in nature, with high-grade dysplasia, and are more aggressive than sporadic adenomas. Certainly metachronous colorectal cancers arising from mutations in HNPCC genes may develop within 2–5 years of a negative colonoscopic screening examination[30]. The time taken for the adenoma to carcinoma sequence is probably determined by the precise genetic mutations involved[31].

Characteristics of metachronous colorectal cancers

Characteristics of the index cancer

It is believed that there is a tendency for metachronous large bowel cancers to arise in patients with index neoplasms of a more favourable Dukes stage, histological grade and prognosis[1,11]. In the Mayo Clinic series[4] of 62 metachronous cancers, 79 per cent of index lesions had no nodal involvement. However, in a large Japanese series[9] only 5·4 per cent of index tumours were classifiable as early among those who later developed metachronous colorectal cancer. Rennert *et al.*[23] and Heald[32] believe the more favourable staging of index cancers is simply a reflection of mortality selection bias.

Dukes stage of metachronous colorectal cancers

The Dukes stage and histological differentiation of metachronous colorectal cancers at diagnosis are no worse than for single tumours. However, some studies have reported generally more favourable tumours[14,23,32–34]. Cali *et al.*[15] state that metachronous colorectal cancers are more likely to be local disease with a lower propensity to distant metastasis than index cancers. This is disputed by others [4,16,24,35,36].

Distribution

Metachronous cancers may occur anywhere in the large bowel. While in many series there is a predominance of right-sided lesions[4,15,23,37,38], in others the distribution is even throughout the colorectum[14,39]. Svendsen *et al.*[40] noted that the relative risk of developing metachronous colorectal cancer was highest in the right colon and diminished towards the rectum. Only one study has reported a predominance of left-sided metachronous cancers[35] and two reports have suggested a similar distribution to single cancers[6,32]. When considering the distribution of metachronous lesions it should be appreciated that up to 60 per cent of colorectal cancers are found below the descending–sigmoid colon junction[41]. It is conceivable that the greater numbers of left colonic resections may increase the likelihood of subsequent metachronous cancers developing in the right colon. Furthermore, right-sided metachronous cancers, especially in a young cohort of patients, may represent unidentified cases of HNPCC syndrome[40].

Aggressiveness of metachronous cancers

Four papers report a greater aggressiveness of metachronous cancer compared with the index lesion[4,23,24,42]. However, many authors emphasize that the second colorectal cancer exhibits the same (certainly no worse) behaviour as the index cancers[14,23,32,33].

Risk factors for metachronous colorectal cancer

Previous colorectal cancer

Where a synchronous cancer is resected along with the index tumour, the cumulative risk of developing a subsequent metachronous neoplasm rises from 3·5 per cent for a single cancer to more than 8 per cent for two cancers[32]. Following excision of a metachronous colorectal cancer, the risk of further metachronous cancers is also increased[12]. Agrez *et al.*[4] reported third subsequent cancers in seven (11 per cent) of 62 patients with metachronous cancer.

Polyps

The risk of metachronous colorectal cancer is double in those with synchronous polyps associated with the primary cancer[1,7,11,43]. Luchtefeld *et al.*[44] reported a 71 per cent incidence of synchronous or interval adenomatous polyps with metachronous colorectal cancers. The incidence quoted in the St Mark's series[45] was 60 per cent and in the Mayo clinic series[4] 40 per cent. A 6·5 per cent frequency of metachronous large bowel cancer in those with synchronous polyps associated with the index cancer compared with 3·4 per cent in those without polyps was demonstrated by Chu *et al.*[36]. Moreover, patients with synchronous polyps less than 30 cm from the index lesion are more likely to develop metachronous adenomatous polyps, compared with those with polyps more distant from the index lesion[46].

Multiple polyps are associated with a higher risk of metachronous colorectal cancer than single polyps[6,39]. The number of polyps is larger with metachronous than with synchronous cancers[39,47–49] and in late, compared with early, metachronous cancers[14]. Over 50 per cent of metachronous cancers are associated with polyps of the tubular adenoma variety; about 10 per cent occur with villous adenomas[32]. The impact of repeated polypectomy on the subsequent occurrence of metachronous colorectal cancer remains to be evaluated[50].

Hereditary non-polyposis colorectal cancer

A propensity for metachronous and synchronous colorectal cancers with a predilection for the proximal colon and development of cancer at an early age are well recognized characteristics of HNPCC[83], a wide spectrum cancer susceptibility syndrome inherited as an autosomal dominant trait with a high penetrance of around 90 per cent[51]. Diagnosis is based on minimal criteria (the Amsterdam criteria) recommended by the International Collaborative Group in HNPCC[52]. These are (1) at least three relatives with histologically verified colorectal cancer, one of whom must be a first-degree relative of the other two; (2) at least two generations affected; and (3) at least one of the cases of colorectal cancer must be diagnosed before the age of 50 years.

Age

Several authors have reported a younger age at first colorectal cancer for those who subsequently develop another large bowel tumour[7,11,24]. In a group of patients with colorectal cancer under 40 years of age, the calculated risk of developing a metachronous colorectal cancer was 16–29 times greater than that of developing a primary cancer[40]. The authors[40] suggested that metachronous colorectal cancer in young patients may be an expression of the HNPCC syndrome. Indeed, in most series the age at diagnosis of the first tumour is comparable to that of single cancers[23] and the patients with metachronous cancer are generally older[6,23,53]. To date, younger age for index cancer is not a prognostic factor for metachronous cancer, but it is of diagnostic value with respect to HNPCC.

Sex

Most studies report no sex difference in metachronous colorectal cancer[2,23,24,54]. Sex has no known influence on the risk of developing a metachronous colorectal cancer[40].

Race

Only one study has considered the question of race, comparing Caucasians with American blacks; no firm conclusions were drawn[23].

Detecting metachronous colorectal cancers

Some studies have reported that regular follow-up and surveillance for metachronous cancer have resulted in the detection of early cancers with a greater potential for resectability[1,13,35]. While Enker and Dragacevic[35] were able to show a higher yield of asymptomatic and early lesions in those followed up for metachronous cancer than in those without follow-up, others have not found a significant difference in the number of curative resections in these groups[55].

Gerdes[56] advocated surveillance at intervals of 2 years for metachronous adenomas, whereas Spigelman[57] endorsed a single colonoscopy to exclude synchronous lesions and subsequent colonoscopic surveillance at intervals of 3 years only in those who are found to have adenomatous polyps.

Treatment of metachronous colorectal cancer

Metachronous colorectal cancers are usually suitable for further curative surgery. An operability of 61 per cent in a very young cohort of patients[8] and a curability rate of 81 per cent[9,39] have been reported. Only 5 per cent in a Japanese series[9] and 6 per cent in a series from St Mark's Hospital, London[45] were deemed inoperable.

Several authors suggest extensive resection for the prevention and treatment of metachronous cancer[33,35,36,42,58,59]. The alternative option of a conventional resection with regular examination of the colon is deemed appropriate[1,32,39,60,61]. Synchronous malignancy in different lymph drainage areas seems a justifiable indication for total colectomy with ileorectal anastomosis, whether at the time of treatment of the index or the metachronous cancer[24,62]. The potential benefit of a radical resection needs to be weighed against a significant morbidity and mortality rate. An individualized approach tailored to suit each patient should be adopted.

While total colectomy eliminates the need for colonoscopic surveillance, vigilance in examining the rectum is still required[63]. Of 17 HNPCC-related patients with colorectal cancer treated by total colectomy, four developed rectal metachronous tumours[64].

Survival

Survival from metachronous colorectal cancer appears not to differ from that associated with single cancers[11]. Stage for stage the prognosis for index and metachronous cancers is largely the same[4,8,11]. The 5-year survival rate after radical resection for multiple cancers in the St Mark's Hospital series was 66 per cent[45], compared with 66·5 per cent in the Japanese series[9] and around 50 per cent in most other reports[2,4,36,39]. The lowest reported survival figure is 20 per cent[14]. The main influence on survival is the stage at diagnosis of the metachronous cancer[23]. Early asymptomatic detection, therefore, offers a potential for improved outcome[35,55,65].

Advances in molecular biology and metachronous colorectal cancer

Individuals with metachronous large bowel cancer show evidence of genetic instability in the cancer, compared with sporadic cancers[53]. Genetic instability can be demonstrated by the accumulation of numerous genetic alterations, particularly in simple repeated non-coding sequences known as microsatellite DNA[71,72]. This phenotype is known as microsatellite instability (MIN) or replication error, and is a characteristic of 92 per cent of cancers from patients with HNPCC[73].

Genetic predisposition to colorectal cancer in HNPCC is due to inherited mutations in genes that control DNA mismatch repair. This DNA repair system serves to correct mistakes that may arise in DNA during its replication[74]. So far, inherited mutations have been identified in four DNA mismatch repair genes (*hMSH2*[66–68], *hMLH1*[70], *hPMS1*[69] and *hPMS2*[69]). Other genes, such as *GTBP*[75], which are involved in the mismatch repair pathway are known.

Thibodeau *et al.*[71] described type I mutations (instability at multiple loci) and type II mutations (instability at one or two loci) in colorectal cancers of the proximal colon. The degree of MIN tends to be very high in cancers from patients with HNPCC[73]; almost every microsatellite locus tested shows instability. Work with cell lines has shown that mutations in *GTBP* result in a low level of MIN[76].

Between 6·5 per cent[77] and 28 per cent[71] of sporadic cancers show MIN, and somatic mutations in the DNA mismatch repair genes have been identified in some of these cancers[78]. However germline mutations in the mismatch repair genes have been found in apparently sporadic colorectal cancers that show MIN[79]. Some reports suggests that MIN-positive sporadic cancers have a high level of instability[79] while others conclude that the level may be low[80].

It may be that the variable degree of MIN is due to different mutations in the DNA mismatch repair genes. So, although MIN appears to be a good indicator of mutation in the DNA mismatch repair genes, there is as yet no correlation between particular mutations and clinical phenotype[73]. In patients with metachronous colorectal cancer in whom instability was detected in the primary cancer, it was also detected in the metachronous cancer[53]. Similarly, when the index cancer did not show instability, neither did the metachronous cancer. The role of MIN as an indicator of metachronous colorectal cancer is under investigation. One study[53] affirmed its value while another did not[81]. A recent study[82] has confirmed that colonoscopic biopsies may be used for MIN analysis. Preoperative information about MIN status may have a role in assessing the risk of developing metachronous colorectal cancer and in the planning of the extent of surgical resection.

Conclusion

It is essential that the colon is scrupulously examined visually before operation for synchronous lesions and that appropriate surgical management is defined. When this is technically not feasible, for instance because of an obstructing carcinoma, a good quality double-contrast enema is an option, provided a postoperative colonoscopy is scheduled. When synchronous lesions are in the vicinity of the index cancer, conventional radical resection followed by regular colonoscopic surveillance is the accepted practice. For distant synchronous lesions, therapeutic endoscopy is a useful adjunct although, for large polyps or carcinomas or rapidly recurring metachronous lesions, a total colectomy and ileorectal anastomosis should be considered seriously in selected patients with a satisfactory sphincter mechanism. This radical approach is a safe option in those with established evidence, based on family history or genetic testing, of the HNPCC syndrome.

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Digest

For this quarter's digest, Professor Christian Herfarth and Dr Thomas Lehnert have selected the best from the October to December 1997 issues of *Der Chirurg*. A digest for the BJS for the same period, written by Mr Colin Johnson, appears in the German journal.

This quarter's digest reviews articles addressing multiple trauma (four articles) and minimally invasive techniques in orthopaedic surgery (four articles) in recognition of the Annual Meeting of the German Society of Trauma Surgery, while a series of seven articles has been commissioned to provide a comprehensive overview of currently applied techniques in inguinal hernia surgery. In his editorial Shumpelick[1] takes a critical look at aggressive marketing and operations designed to suit all types of inguinal hernias. He calls for a problem-oriented approach for which Shouldice repair, preferably under local anaesthesia, should provide a reliable and minimally invasive repair for most inguinal hernias, primary or recurrent. Implantation of alloplastic material should be reserved only for very large hernias.

Carcinoma of the pancreas

Cancer of the head of the pancreas is traditionally treated by Whipple's partial pancreatoduodenectomy, if complete macroscopic tumour removal appears feasible. The operation carries postoperative sequelae which are partly related to loss of pyloric function and duodenal transit. Theoretically this may be overcome by pylorus-preserving partial pancreatoduodenectomy. The operation has proven useful for patients with chronic pancreatitis, but its applicability and long-term results in patients with ductal pancreatic cancer have been studied only in a few patients. Further arguments in favour of pylorus preservation are reduced operating time and blood loss, while concerns exist regarding radicality of local tumour resection.

The group from Ulm[2] presents their experience with 130 patients with ductal carcinoma of the pancreas treated between May 1990 and April 1995. A standard Kausch–Whipple operation was performed in 61 patients and 69 patients had a pylorus-preserving partial pancreatoduodenectomy. Data were collected prospectively, although this was not a randomized study. The distribution of men and women was similar for both groups and median age was 59 years (Whipple) and 61 years (pylorus-preserving operation). Mean(s.d.) operating times were longer for standard Whipple's procedure (405(60) min) compared with 360(35) min for pylorus preservation ($P < 0.001$). Intraoperative blood loss was a median of 3·1 litres for Whipple's operation *versus* 2·2 litres for pylorus-preserving partial duodenopancreatectomy ($P < 0.001$) and the latter required fewer perioperative blood transfusions. The postoperative morbidity rate was identical at 39 per cent for both groups. Thirty-day mortality rates of 2 and 3 per cent respectively were also not significantly different between the groups. Return to a normal diet was somewhat slower in the group in which the pylorus was preserved, but overall no significant difference was observed when the two groups were compared. Histopathological evaluation indicated that in the pylorus-preservation group slightly more patients were stage I (35 *versus* 23 per cent) and fewer patients were stage III (59 *versus* 69 per cent), although lymphadenectomy yielded more lymph nodes in the pylorus-preservation group (mean(s.d.) 27(5) *versus* 20(4) lymph nodes per specimen in the Whipple group). Median survival for stage I pancreatic carcinoma was 32 months after Whipple's procedure and 36 months after pylorus-preserving partial pancreatoduodenectomy. In stage III survival was 10 and 11 months respectively. The authors conclude that pylorus-preserving partial pancreatoduodenectomy allows for radical lymphadenectomy and is similarly successful regarding oncological long-term results. It should not be used for tumours close to the pylorus or postpyloric duodenum, but appears to be advantageous for other locations of pancreatic cancer, as the operation is technically easier, speedier and causes less blood loss.

Intensive care jaundice

It is a well recognized phenomenon that many patients requiring intensive care treatment for severe disease or postoperative complications develop jaundice without apparent involvement of the liver or bile ducts in the initial disease process. Surgeons from Frankfurt have undertaken to document prospectively all patients admitted to their intensive care unit (ICU) between December 1991 and November 1992, in an attempt to quantify the incidence of postoperative jaundice and determine its prognostic significance[3]. Patients were admitted from the general, urological and cardiovascular surgical services as were trauma patients and those undergoing orofacial surgery. During a 12-month period a total of 1572 patients were recorded. Patients undergoing operative treatment for or with pre-existing diseases of the liver, bile ducts or pancreas were excluded, leaving a total of 1275 patients for study. Standardized documentation used directly computer-readable forms to collect 2000 parameters per patient and day. Thus a total of 5·2 million individual parameters were obtained for statistical analysis.

Ninety-seven of 1275 patients admitted to the ICU developed a serum bilirubin level of 2 mg/dl or higher and were eligible for detailed analysis. Median length of stay of jaundiced patients was 15 (range 2–59) days compared with 2 (range 1–39) days in non-jaundiced patients. Twenty-eight (29 per cent) of 97 jaundiced patients died compared with 28 (2·4 per cent) of 1178 non-jaundiced patients. When several parameters related to disease severity such as septic organ failure score, multiple organ failure score, positive end-expiratory pressure ventilation, central venous pressure, low systolic arterial pressure (less than 90 mmHg for more than 120 min) and others were compared between jaundiced and non-jaundiced patients the latter had significantly higher readings, but the Acute Physiology And Chronic Health Evaluation II score was not different between the two groups of patients. Maximum bilirubin levels and maximum daily increase in bilirubin levels were both inversely related to outcome.

Interestingly, raised liver enzyme levels were recorded with almost equal frequency in both groups. Hyperbilirubinaemia was most frequently observed in patients with multiple trauma (14 of 34 patients) and patients undergoing vascular surgery (13 of 105, 12 per cent). Overall mortality rate was higher in jaundiced patients, but calculation of predictive values, sensitivity and specificity revealed that postoperative intrahepatic cholestasis was not a reliable prognostic indicator.

Complications of minimally invasive surgery

Pneumoperitoneum and intraoperative reverse Trendelenburg positioning of patients undergoing minimally invasive surgery may cause hypercoagulability and peripheral venous stasis with a subsequently increased risk of venous thrombosis. Baca and associates[4] have performed a prospective randomized controlled trial to determine whether low-risk patients benefit from postoperative treatment with low molecular weight heparin. Patients were eligible for the study if they were scheduled for laparoscopic cholecystectomy or appendicectomy. Patients having more than three of the risk factors (Broca Index over 130, smokers, past history of venous thrombosis, use of oral contraceptives) were considered at increased risk for venous thrombosis and were excluded, as were patients having epidural anaesthesia. Patients in the treatment group received low molecular weight heparin once daily starting on the day of the operation for at least 6 days. Patients in the control group received physiotherapy and compression stockings as did patients in the treatment group, but not low molecular weight heparin. Endpoints of the study were clinical venous thrombosis or pulmonary embolism. Interim analysis was performed after 500 patients had been randomized.

A total of 719 patients were randomized from 33 hospitals. One patient was excluded because of incomplete documentation leaving 359 each in the treatment and control groups. Mean(s.d.) age was 48(15) years in the treatment group and 45(16) years in the control group. The majority of patients were female in both groups (75 per cent), and 85 per cent (control) and 93 per cent (treatment) of patients had cholecystectomy. All except two patients had general anaesthesia. A total of 23 patients were suspected to have developed either venous thrombosis or pulmonary embolism. Additional diagnostic procedures (duplex scan, phlebography) confirmed the diagnosis in only two patients. Both had received low molecular weight heparin. Fifteen of 718 patients required conversion to open surgery and three underwent reoperation. No significantly increased incidence of intraoperative or postoperative bleeding, wound haematoma or other complications was noted in the treatment group. Because the frequency of study events was lower than anticipated the review committee decided that it was unlikely that a significant difference would be detected and the study was closed prematurely after 719 patients had been admitted; the planned number was 1000 patients. The authors conclude that in a low-risk group of patients postoperative low molecular weight heparin is not warranted after limited minimal access cholecystectomy or appendicectomy.

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Laparoscopic subtotal cholecystectomy in patients with complicated acute cholecystitis or fibrosis

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Background The open subtotal cholecystectomy technique has simplified removal of the difficult gallbladder. Increasing laparoscopic experience has made laparoscopic subtotal cholecystectomy (LSC) a feasible option in patients with complicated acute or chronic cholecystitis.

Methods LSC was performed in 29 patients with severe inflammation or fibrosis of the gallbladder associated with gallstone disease over a 23-month period. These 29 patients (mean age 53 years; 22 women) constituted 8·5 per cent of the total number of laparoscopic cholecystectomies performed ($n = 340$) and 15·6 per cent of 186 patients with acute cholecystitis. Eighteen patients in the latter group underwent conversion to open cholecystectomy. The indications for LSC were acute cholecystitis/empyema ($n = 23$) and severe fibrosis ($n = 6$).

Results The cystic duct was either clipped before division ($n = 15$), sutured ($n = 2$) or ligated using an Endoloop ($n = 10$). In two patients the gallbladder bed was drained without isolating the cystic duct. The posterior wall of the gallbladder was left intact to avoid excessive bleeding or damage to bile ducts in the gallbladder bed. A suction drain was inserted in 14 cases. Median operating time was 73 (range 45–130) min. One patient died after operation from a myocardial infarction. Six patients had local complications (two haematomas, three bile leaks, one minor wound sepsis) and nine developed respiratory infections. Median hospital stay was 5 (range 2–28) days.

Conclusion LSC is a safe, relatively simple and definitive procedure allowing removal of a difficult gallbladder and reducing the need for open conversion or cholecystostomy in the majority of patients.

The risk of bile duct injury during a standard cholecystectomy is greatest while dissecting in Calot's triangle, particularly in the presence of severe inflammation or fibrosis of the gallbladder[1]. Open subtotal cholecystectomy which was described by this group in 1985[2] has proven to be a safe, simple and definitive procedure in this situation[3–5]. Increasing laparoscopic experience and sophisticated techniques have made laparoscopic subtotal cholecystectomy (LSC) a feasible option[6]. This study describes the technical aspects and evaluates the results of LSC in the management of complicated acute and chronic cholecystitis.

Patients and methods

Patients who underwent laparoscopic cholecystectomy during the 23-month period from January 1994 to November 1995 were studied. Subtotal cholecystectomy was performed only on patients with severe inflammatory or fibrotic changes in Calot's triangle. Preoperative biliary investigations included liver function tests and ultrasonography. Endoscopic retrograde cholangiopancreatography (ERCP) was performed on patients in whom common bile duct (CBD) stones or other bile duct disease was suspected because of symptoms (e.g. jaundice, pancreatitis), raised alkaline phosphatase and bilirubin levels or dilated CBD on ultrasonography.

Laparoscopic technique

A standard laparoscopic approach was used. After division of adhesions to the anterior surface of the gallbladder, the cystic duct–Hartmann's pouch junction was identified by blunt dissection using a suction–irrigation (hydrodissection) technique. When feasible, the cystic duct and artery were clipped or ligated and divided in the standard fashion (*Fig. 1*). If this was not possible, or in cases with stone impaction, the gallbladder was incised at the level of Hartmann's pouch and divided circumferentially (*Fig. 2a*) which then allowed prograde dissection and isolation of the cystic duct with an Endoloop (Ethicon, Edinburgh, UK) (*Fig. 2b*). When isolation of the cystic duct was not possible, a purse-string suture was inserted in Hartmann's pouch or, when there was no evidence of bile leak, the gallbladder bed was simply drained after subtotal removal of the gallbladder.

Subtotal removal of the gallbladder was performed when the gallbladder was entered inadvertently or excessive bleeding occurred because of difficulty in finding a plane of dissection between the gallbladder and liver bed. Excision of the gallbladder was performed using electrocoagulation (hook dissector or scissors) at the gallbladder–liver bed junction leaving the smallest possible strip of posterior gallbladder wall. Destruction of the residual gallbladder mucosa with electrocoagulation was optional. Great care was taken to remove all spilled stones using a 'spoon' forceps and to wash the peritoneal cavity with a suction–irrigation system.

Results

Twenty-nine patients underwent laparoscopic subtotal cholecystectomy during the 23-month period. Mean age

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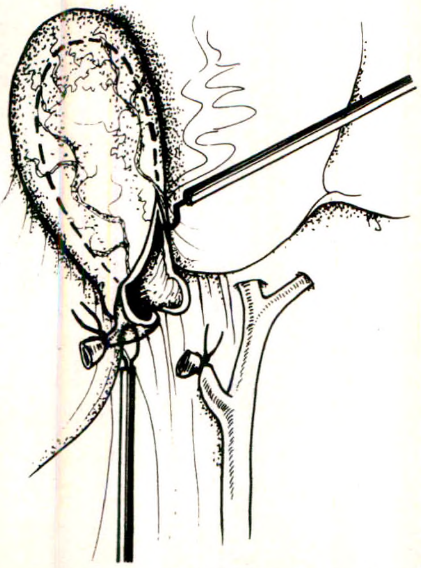

Fig. 1 Cystic duct ligated and divided in the standard fashion. Beginning of subtotal excision of the gallbladder

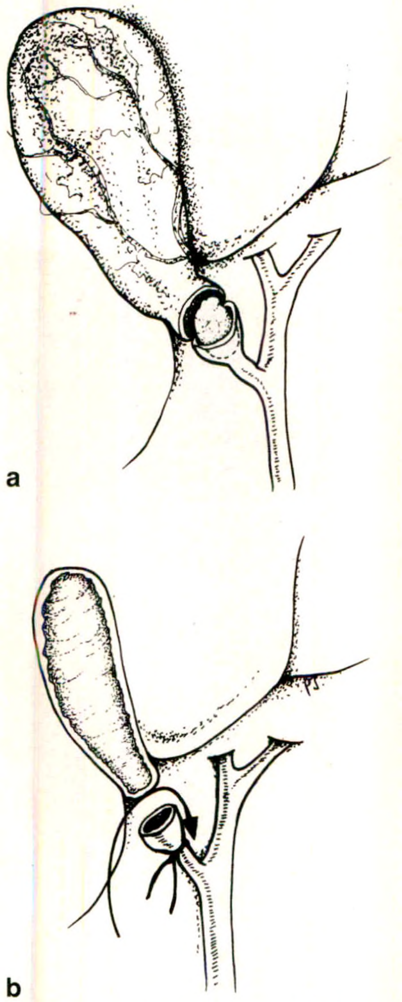

Fig. 2 **a** Gallbladder incised at the level of Hartmann's pouch with stone impaction. **b** Prograde dissection and isolation of cystic duct with Endoloop and subtotal removal of the gallbladder

was 53 (range 19–81) years; 22 were women. These patients constituted 8·5 per cent of the total number who underwent laparoscopic cholecystectomy ($n = 340$) and 15·6 per cent of patients with acute cholecystitis ($n = 186$). Twenty-four of the 340 patients underwent conversion to open cholecystectomy of whom 18 had acute cholecystitis. Five of the converted patients had an open subtotal cholecystectomy. In 23 patients LSC was performed for acute cholecystitis/empyema (four with Mirizzi type 1 syndrome) and six had severe fibrosis. In 15 patients the cystic duct and artery were clipped before division (*Fig. 1*). In 12 the gallbladder was incised at Hartmann's pouch (*Fig. 2*) and the cystic duct was sutured ($n = 2$) or ligated using an Endoloop ($n = 10$). In two patients the gallbladder bed was drained without isolating the cystic duct. CBD stones or stenoses were suspected before surgery on clinical, biochemical and ultrasonographic criteria in six of 29 patients. Four of the six underwent ERCP before surgery and in two of the four patients CBD stones were extracted. In the remaining two patients endoscopic retrograde cholangiography failed and both subsequently had negative intraoperative cholangiography. No other patient had intraoperative cholangiography. A suction drain was inserted in 14 cases.

Median operation time was 73 (range 45–130) min. There was one death; a 69-year-old woman died from a necropsy proven myocardial infarction 48 h after operation. Six patients had local complications: one had minor umbilical port sepsis, one patient had a self-limiting bile leak after simple drainage and four patients had subhepatic collections (two bile, two haematomas). Two of these required percutaneous ultrasonographically guided catheter drainage. All three bile leaks occurred in patients with acute cholecystitis in whom the cystic duct stump was secured with metal clips. Nine patients developed respiratory infections. Mean hospital stay was 5 (range 2–28) days. The extended hospital stay in one patient was due to prolonged catheter drainage from a liver abscess which was a complication of acute cholecystitis.

Discussion

Laparoscopic cholecystectomy is technically feasible in the majority of patients with acute cholecystitis but compared with elective operation the conversion rate to open surgery is higher and the operative time longer[7,8], with an increased risk of bile duct injury[9]. This series confirms the feasibility and safety of performing subtotal cholecystectomy laparoscopically thus avoiding the need for cholecystostomy or conversion to open operation in most patients. In some respects the laparoscopic approach may have certain advantages over the open technique. The operative view and approach to Calot's triangle is superior, allowing easier identification and isolation of the cystic duct–Hartmann's pouch junction which is the key to safe cholecystectomy. With the open technique this manoeuvre is more difficult and often requires the use of a purse-string closure technique from within the gallbladder, increasing the risk of bile leakage once the inflammatory process has resolved[1].

The hydrodissection technique using the blunt tip of the suction–irrigation apparatus was used when tissue was friable and inflamed to define and isolate the cystic duct, and to identify the anatomy at the cystic duct–Hartmann's pouch junction. However, the dissection may be more difficult when there is stone impaction in Hartmann's pouch and in cases of Mirizzi syndrome. In this situation removal of the stone by incising the site of stone impaction allows isolation of the cystic duct by continuing the incision into the posterior wall under direct vision in a circumferential fashion. Prograde dissection keeping close to the cystic duct or gallbladder wall allows secure placement of an Endoloop. This manoeuvre avoids leaving residual Hartmann's pouch while minimizing the risk of injury to the common or right hepatic duct. In cases where cystic duct isolation is impossible, placement of a drain will establish a controlled bile leak should this occur. Such bile leaks usually resolve spontaneously. If the leak persists, endoscopic sphincterotomy with or without temporary bile duct stenting is generally successful[10,11].

In this series the majority of operations were performed with the initial purpose of total removal of the gallbladder and were only converted to the subtotal technique when dense inflammation or fibrosis resulted in either inadvertent entry into the gallbladder, or when excessive bleeding occurred from the gallbladder bed. Great care was taken to remove all spilled stones with the use of a spoon forceps. An important aspect of the technique was to excise as much of the gallbladder as possible, leaving only a small residual strip of posterior wall. The liberal use of electrocoagulation with a hook dissector or scissors provided adequate haemostasis. Care must be taken to avoid excessive coagulation close to Calot's triangle. Leaving a strip of posterior gallbladder wall avoided inadvertent damage to the ducts of Lushka or superficial bile ducts in the gallbladder bed with resultant postoperative bile leak.

As with the open subtotal technique[2], the incidence of subhepatic collections afer LSC was low, considering that the majority of patients presented with acute cholecystitis; bile leaks from the cystic duct stump did not result in major complications. However, the use of a ligature is advised in the presence of acute cholecystitis to avoid the problem of dislodgement. We believe that preoperative ERCP should be mandatory in patients with severe cholecystitis in whom bile duct stones are suspected. In these cases extraction of CBD stones via the transcystic route is not usually feasible and laparoscopic exploration of the bile duct may be hazardous in the presence of severe inflammation

LSC is feasible in the majority of cases when total removal of the gallbladder is not possible in acute cholecystitis or when there is severe fibrosis. The procedure is safe, has an acceptably low morbidity rate, and reduces the need for either laparoscopic or percutaneous cholecystostomy or conversion to open cholecystectomy.

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Management of hepatobiliary and pancreatic *Ascaris* infestation in adults after failed medical treatment

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Background The roles of endoscopy and surgery in the management of *Ascaris lumbricoides* affecting the hepatobiliary and pancreatic system in adults were determined.

Methods All patients undergoing endoscopic retrograde pancreatography for ascariasis of the biliary or pancreatic system unresponsive to standard medical therapy were analysed. Worms were extracted using snare, Dormia basket or biopsy forceps. Success was defined as clearance of worms and eradication of symptoms.

Results Endoscopic extraction was performed in 25 patients with success in 19. Failures occurred in one patient with *Ascaris* in the gallbladder, and in five with associated strictures or stones. All six patients were treated successfully by surgery.

Conclusion Endoscopy was successful in the treatment of *Ascaris* infestation resistant to medical therapy in 19 of 25 patients. Surgery remains important in the management of infestations complicated by biliary or pancreatic strictures and stones, or worms in the gallbladder.

Ascaris infestation is often asymptomatic and most complications arise in children. At the Red Cross Children's hospital in Cape Town 20 per cent of acute paediatric admissions are directly due to *Ascaris* infestation and 70 per cent of children within the hospital were found to be carriers of *Ascaris*[1]. Surgical presentation usually results from massive infestation resulting in intestinal obstruction, volvulus or intussusception[2] with hepatobiliary and pancreatic *Ascaris* (HPA) being less common, accounting for only 10–19 per cent of *Ascaris*-related admissions[3,4].

Emergency admissions for HPA in adults are uncommon even in endemic areas and although worms appear to migrate frequently through the ampulla of Vater and into the common bile duct (CBD)[5] most appear to return spontaneously to the intestine[6,7]. Occasionally an ascarid (which may reach 15 cm in length) entering the CBD may cause a mechanical obstruction or result in spasm of the sphincter of Oddi resulting in obstruction. The main pancreatic duct (MPD) itself is rarely the site of *Ascaris* migration presumably because of its narrow calibre, and pancreatitis is usually secondary to invasion of the CBD causing obstruction of the ampulla of Vater and pancreatic duct[8]. The diagnosis is usually made by ultrasonographic identification of an ascarid within the CBD or MPD giving the typical 'bull's eye' appearance[9].

With increasing ease of travel and the movement of refugees, cases of hepatobiliary ascariasis are appearing in developed world countries[10–15]. Surgery has been regarded as the standard treatment when medical therapy has failed[4,16,17], and apart from short case reports[18,19] experience with endoscopic management is limited to a single series[20]. This paper reports the management of complicated HPA in adults unresponsive to standard medical therapy.

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Patients and methods

From January 1986 to December 1995, 25 patients with hepatobiliary or pancreatic *Ascaris* infestations failed to respond to standard medical therapy. Mean age was 31 (range 14–80) years with a sex distribution of 22 women and three men. The majority of patients were from black townships (22 black, three white patients). Many patients were tertiary referrals having undergone failed medical treatment elsewhere. All patients were admitted to hospital and given symptomatic treatment which included cessation of oral intake, intravenous fluids, analgesia, anticholinergic antispasmodic agents (hyoscine butylbromide 20 mg four times daily), antihelmintics (mebendazole 100 mg twice daily) and antibiotics if cholangitis was present. Ultrasonography was performed on admission and endoscopic retrograde cholangiopancreatography (ERCP) was performed if symptoms failed to improve within the first week.

Worms were sometimes seen at endoscopy protruding through the ampulla of Vater (*Fig. 1*). When not directly visible they were

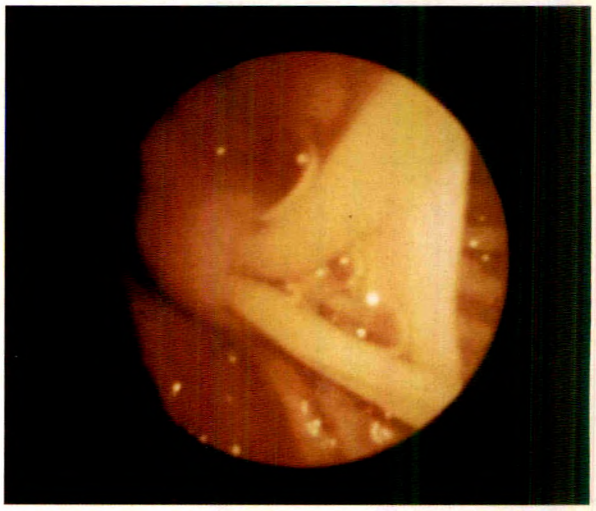

Fig. 1. Endoscopic view of ascarid emerging from the ampulla

demonstrated by ERCP after cannulation of the biliary or pancreatic ducts (*Fig. 2*). When worms were confirmed, extraction was attempted with a snare, Dormia basket or grasping forceps. Once engaged in the snare or forceps, worms were pulled out of the ampulla into the duodenum, and the duodenoscope subsequently withdrawn through the mouth with the worm. Care was required not to transect the worm by overtightening of the snare. When ERCP was unsuccessful surgery was performed. Patients were followed up clinically and with ultrasonography or ERCP to ensure successful worm eradication.

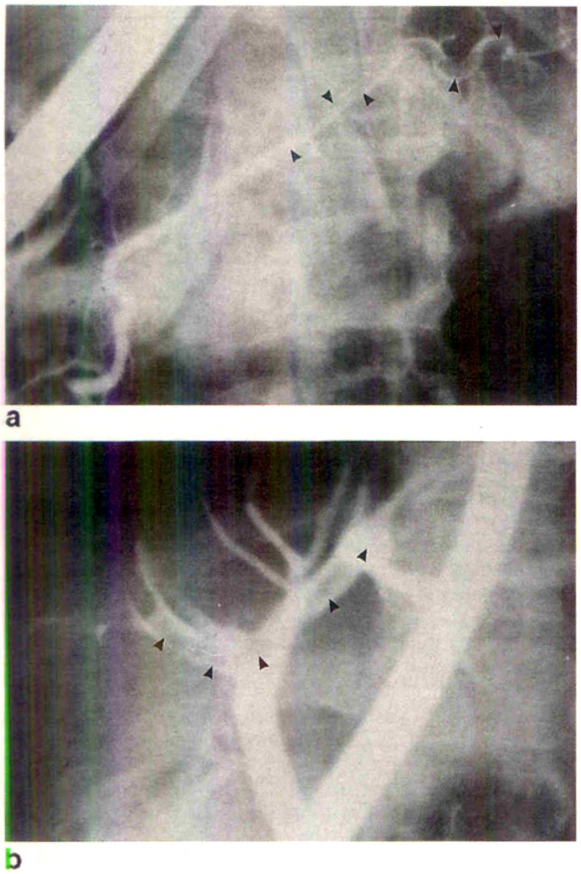

Fig. 2. Endoscopic retrograde pancreatography of ascarids (arrows) in **a** main pancreatic duct and **b** intrahepatic ducts

Results

Presentation

In this series HPA presented in four clinical forms: cholangitis ($n = 8$) (right hypochondrial pain, jaundice and high temperature); acute pancreatitis ($n = 8$) (epigastric pain and raised level of amylase); biliary colic ($n = 7$) (epigastric/right hypochondrial pain radiating to the back or shoulder); and painless obstructive jaundice ($n = 2$). Haematological and biochemical indices were non-specific with eosinophilia present in only five patients.

Endoscopic retrograde cholangiopancreatography findings and worm clearance

Worms were commonest in the extrahepatic (15 patients) and intrahepatic (nine patients) ducts and only rarely affected the pancreatic duct (three patients) or gallbladder (one patient). Calculi were present in six patients; in the CBD in three, the intrahepatic ducts in two and the pancreatic duct in one. Three patients had strictures. One extrahepatic biliary stricture was successfully dilated; one intrahepatic and one pancreatic duct required surgery.

Successful worm clearance was achieved in 19 patients with a median of one procedure; nine patients had more than one procedure with a maximum of five procedures. Endoscopic sphincterotomy was required in eight cases, seven biliary and one pancreatic. In five it was performed to remove stones co-existing with worms (including one pancreatic duct stone), in one because of a choledochoduodenal fistula and in two to facilitate removal of worms. Two complications may have been attributable to or exacerbated by ERCP: an empyema of the gallbladder in a patient on warfarin with myocardial ischaemia in whom multiple ERCPs were performed during removal of stones and ascarids; and a pancreatic pseudocyst in a patient with acute pancreatitis after attempts to remove a worm from the pancreatic duct.

Surgery

Worm extraction failed in six patients who underwent the surgical procedures listed in *Table 1*. There was no associated morbidity or mortality with these procedures.

Table 1 Operative management following failed extraction of *Ascaris lumbricoides* by endoscopic retrograde pancreatography

Patient	Age	Sex	No. of ERCPs	Indication	Operation
1	42	F	1	Trapped gallbladder ascarid	Laparoscopic cholecystectomy[29]
2	71	F	5	Empyema ? secondary to multiple ERCPs	Open cholecystectomy with exploration CBD
3	24	F	1	Persistence of three ascarids	Exploration of CBD with direct closure
4	70	M	3	Dead ascarids within CBD and left intrahepatic ducts and intrahepatic stones	Exploration of CBD with hepaticojejunostomy
5	26	F	2	Left hepatic duct stricture with intrahepatic ascarids	Exploration of CBD with hepaticojejunostomy access loop[30]
6	23	F	2	Main pancreatic duct stricture with proximal calculi and ascarid	Longitudinal pancreaticojejunostomy

ERCP, endoscopic retrograde cholangiopancreatography; CBD, common bile duct

Discussion

Ascaris lumbricoides is endemic where poverty, overcrowding, poor sanitation and an unsafe water supply exist, and involves around 155 million Africans[21]. Adult worms live in the proximal small bowel of humans and fertilized eggs, excreted in the faeces, may remain dormant for years. Following ingestion, the eggs hatch in the small intestine and penetrate the intestinal wall to enter the portal circulation or lymphatics. They migrate through the liver to the heart, through the pulmonary artery to the lungs where they burrow into the alveoli. Here they moult and migrate into the bronchi and trachea, and enter the oesophagus to return to the intestine again. After two further moultings they become mature adults.

Symptomatic *Ascaris* infestation is uncommon in adults. In this series 22 of 25 patients were women, predominantly young, black and with children. Ova are ingested from the soil and children are thus mostly at risk. Women may be more affected because of their greater contact with children in these communities where the carrier rate among children is around 70 per cent[22].

The majority of patients with pancreatic and biliary ascariasis respond to medical treatment of bowel rest, antispasmodic and antihelmintic drugs, and resolution of symptoms can be expected in 68–80 per cent[1,20]. Worms within the biliary tract are not killed by standard antihelmintic drugs. Pyrantel palmoate has no enterohepatic circulation[23], and mebendazole is poorly absorbed from the intestinal tract, with less than 1 per cent excreted in the bile[24]. Successful treatment appears to depend on worms returning to the small intestine where they are exposed to adequate concentrations of drugs. Failure of medical management may be due to the presence of dead worms, concomitant stones or strictures all of which prevent the worms returning to the duodenum. Since 1986 endoscopic treatment has become the treatment of choice in this unit, with surgery reserved for patients who fail to respond to an adequate trial of medical management or who show evidence of complications.

ERCP was successful in 19 of 25 patients who had not responded to adequate medical treatment. More than one procedure was required in nine patients. Failure was due to inability to reach ascarids in the gallbladder or intrahepatic ducts, or the presence of concomitant strictures preventing clearance of calculi and worms. Sphincterotomy was necessary in eight patients usually for the removal of calculi, and in only two patients was sphincterotomy performed solely for removal of the ascarid. Sphincterotomy should be avoided where possible as it appears to predispose to recurrent infestation by allowing easier access to the ampulla of Vater[25,26]. It is important to prevent reinfestation by administration of antihelmintic drugs although this is not always practicable within the poor social conditions which most of these patients have to endure.

Concomitant biliary stones were present in five patients. The association between *Ascaris* and intrahepatic stones has been noted in South-east Asia[5] and in South Africa[27], and *Ascaris* debris and ova are found in stones from these patients[16,28] supporting the hypothesis that *Ascaris* is one of the causes of intrahepatic stone disease in endemic areas.

Surgery continues to have a place in the management of HPA when endoscopic treatment has failed. Surgery was successful in all six cases and consisted of cholecystectomy in two patients[29], and removal of calculi and worms from the biliary ducts in three patients and pancreatic duct in one patient. Additional drainage procedures (hepaticojejunostomy or pancreaticojejunostomy) were performed in three patients. Recurrent stones have been successfully removed percutaneously via a hepaticojejunostomy access loop[30] on ten occasions in one patient in whom this was performed.

Despite its worldwide prevalence, *Ascaris* involving the pancreatic and biliary ducts is uncommon and usually responds to medical treatment. When this fails endoscopic removal is usually successful and surgery is now reserved for cases complicated by biliary or pancreatic strictures and stones, or worms in the gallbladder.

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Anomalous pancreaticobiliary junction without congenital choledochal cyst

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Background Anomalous pancreaticobiliary junction (APBJ) without congenital choledochal cyst (CCC) carries a high risk of gallbladder carcinoma development. The aim of this study was to obtain information allowing early diagnosis and appropriate management.

Methods The clinical features, imaging findings and surgical outcome of 18 patients with APBJ without CCC were analysed retrospectively.

Results Fourteen patients had symptoms, including those of acute pancreatitis (five patients). In 16 patients the gallbladder showed abnormalities, including carcinoma (eight) and mucosal hyperplasia (11). Ultrasonography detected gallbladder carcinoma with 100 per cent sensitivity and mucosal hyperplasia with 91 per cent sensitivity. A long common channel was demonstrated by endoscopic retrograde cholangiopancreatography (ERCP) in all patients, endoscopic ultrasonography in nine of ten, and magnetic resonance cholangiopancreatography (MRCP) in five of five. Five of eight patients with gallbladder carcinoma underwent extended cholecystectomy with bile duct excision. Three patients with cancer and eight with no cancer had cholecystectomy alone. None developed bile duct carcinoma or acute pancreatitis after operation. All patients without malignancy remained asymptomatic for a mean follow-up period of 4·7 years.

Conclusion Prophylactic cholecystectomy is recommended for patients with APBJ without CCC. For early diagnosis of APBJ, gallbladder abnormalities on ultrasonography or acute pancreatitis of unknown aetiology should prompt further investigation with ERCP or less invasive imaging modalities such as endoscopic ultrasonography and MRCP.

Anomalous pancreaticobiliary junction (APBJ) is a rare congenital anomaly in which the pancreatic and biliary ducts unite outside the duodenal wall and form a long common channel of 15 mm or greater on endoscopic retrograde cholangiopancreatography (ERCP)[1,2]. APBJ is present in nearly all patients with congenital choledochal cyst (CCC)[2–4]. This anomaly is also found in patients without CCC[2–9]. APBJ without CCC is frequently associated with gallbladder carcinoma[2–9]. Therefore, early diagnosis and treatment of APBJ, before a malignancy arises, are essential[8]. APBJ with CCC is easily diagnosed, because typical symptoms (abdominal pain and mass, jaundice) or a dilated bile duct prompt examination with ERCP[10]. However, APBJ without CCC, particularly in the absence of gallbladder carcinoma, is difficult to diagnose because clinical features and imaging findings characteristic of APBJ without CCC have not been well documented. ERCP depicts APBJ most reliably[2], but is invasive and carries a potential for morbidity[11]. Accurate, less invasive, imaging techniques are desirable for diagnosing APBJ. A standard treatment for APBJ without CCC has not been established.

The aims of the present study were: (1) to analyse the clinical and imaging features of APBJ without CCC, to identify clues to early diagnosis; (2) to assess the diagnostic value of minimally invasive imaging modalities including endoscopic ultrasonography[12,13] and magnetic resonance cholangiopancreatography (MRCP)[14–16]; and (3) to analyse the long-term results of surgical treatment. The ultimate goal was to establish an optimal management strategy.

Patients and methods

Between February 1990 and December 1996, 18 adult patients with APBJ without CCC underwent surgical treatment at Kyorin University Hospital and two affiliated hospitals: five men and 13 women with a mean age of 45·9 (range 27–70) years. APBJ was defined as a common channel measuring 15 mm or longer at ERCP.

Before operation these patients underwent ultrasonography ($n = 18$), ERCP ($n = 18$), endoscopic ultrasonography ($n = 10$) and MRCP ($n = 5$). For endoscopic ultrasonography an echoendoscope equipped with a 7·5-MHz rotating transducer (GF-UM2/EU-M2 or GF-UM3/EU-M3; Olympus, Tokyo, Japan) was used. MRCP was performed using a 1·5-T clinical imager (Magnetom-vision; Siemens, Erlangen, Germany) with a phased-array coil. Magnetic resonance cholangiopancreatograms were obtained by using half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequences[15,16].

Clinical presentation, laboratory, imaging and pathological findings, operative management and outcomes were analysed for the 18 patients. Follow-up extended from the date of operation to June 1997 or death (mean 3·3 years (range 7 months to 7 years)).

To provide the total numbers of patients with gallbladder carcinoma and with gallbladder mucosal hyperplasia, medical charts of inpatients at the three hospitals during the same period were reviewed. To determine the incidence of APBJ, ERCP reports were reviewed in the same way.

Results

Clinicopathological features

Of the 18 patients, 14 had symptoms, including abdominal pain (13 patients) and jaundice (2; bile duct invasion by gallbladder ($n = 1$) or pancreatic head ($n = 1$) carcinoma. Mean duration of symptoms before surgical treatment was

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1·1 years (range 1 month to 6 years). Five patients experienced acute mild pancreatitis evidenced by acute onset of upper abdominal pain and threefold increase in serum amylase concentration.

Histological examination of the gallbladder ($n = 18$) revealed adenocarcinoma ($n = 8$; four with and four without mucosal hyperplasia), adenoma ($n = 1$), cholesterol polyp with hyperplasia ($n = 2$), mucosal hyperplasia ($n = 5$) or no abnormality ($n = 2$). All carcinomas were at an advanced stage with invasion to the subserosal layer or beyond. Mucosal hyperplasia was characterized by diffuse proliferation of ordinary gallbladder epithelium with a villous or spongiform pattern (*Fig. 1a*). The gallbladders with hyperplasia showed diffuse, 1·2–5·1 (mean 2·3) mm, mucosal thickening. Four patients (one with and three without gallbladder carcinoma) had cholelithiasis. Two patients without gallbladder lesions had pancreatic carcinoma. Mean age did not differ significantly between patients with gallbladder carcinoma (46·6 years) and those without pancreatobiliary malignancy (39·9 years) ($P = 0·14$, Wilcoxon test). The amylase level in gallbladder bile was raised (range 12 500–589 000 (mean 101 600) units/l) in 12 of 13 patients in whom bile was sampled.

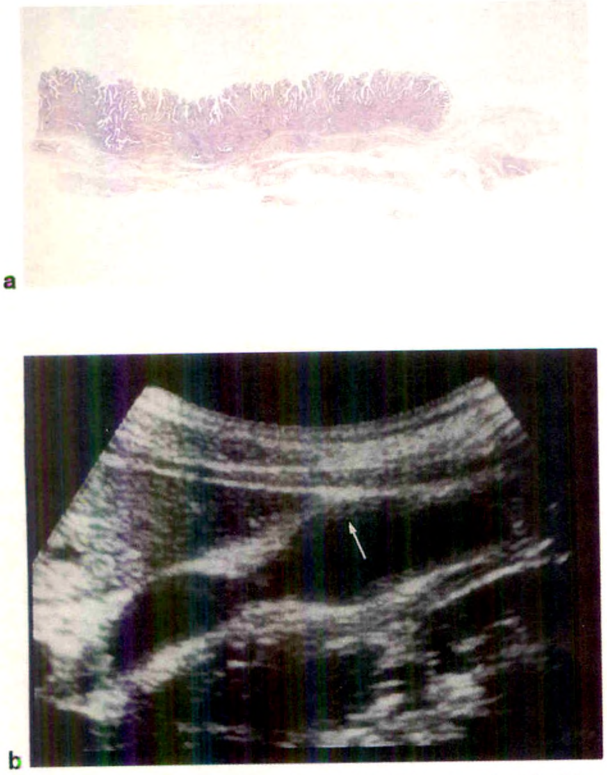

Fig. 1 Mucosal hyperplasia of the gallbladder associated with anomalous pancreaticobiliary junction without congenital choledochal cyst in a 38-year-old woman. **a** Pathological specimen (haematoxylin and eosin staining; original magnification × 4) shows marked villous hyperplasia of the gallbladder epithelium. **b** Ultrasonography shows a 3-mm symmetrical, diffuse, hypoechoic thickening of the inner layer (mucosal layer, arrow) of the gallbladder wall

Table 1 Detection of long common channel and gallbladder lesions by imaging

	Long common channel ($n = 18$)	Gallbladder carcinoma ($n = 8$)	Gallbladder mucosal hyperplasia ($n = 11$)
Ultrasonography	0 of 18	8 of 8	10 of 11
ERCP	18 of 18	3 of 8	3 of 11
Endoscopic ultrasonography	9 of 10	3 of 3	3 of 4
MRCP	5 of 5	0 of 2	0 of 3

ERCP, endoscopic retrograde cholangiopancreatography; MRCP, magnetic resonance cholangiopancreatography

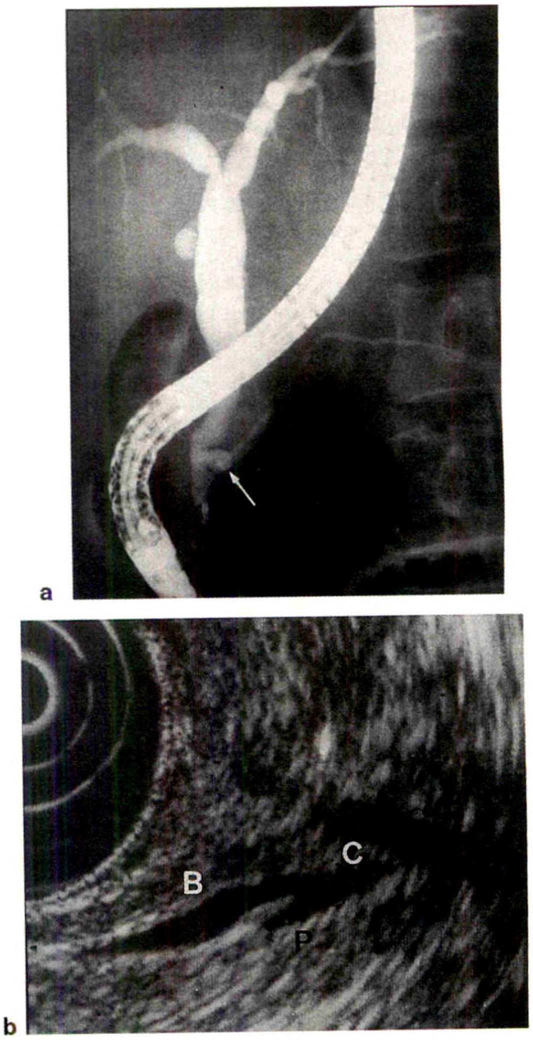

Fig. 2 Anomalous pancreaticobiliary junction without congenital choledochal cyst in a 32-year-old woman. **a** Endoscopic retrograde cholangiopancreatography shows a long common channel; the arrow indicates the pancreaticobiliary junction. **b** Endoscopic ultrasonography demonstrates a long common channel (C), the common bile duct (B) and the main pancreatic duct (P)

Diagnosis

On ERCP, the length of the common channel ranged from 15 to 32 (mean 20) mm, the junction being outside the duodenal wall (*Table 1*; *Fig. 2a*). The diameter of the

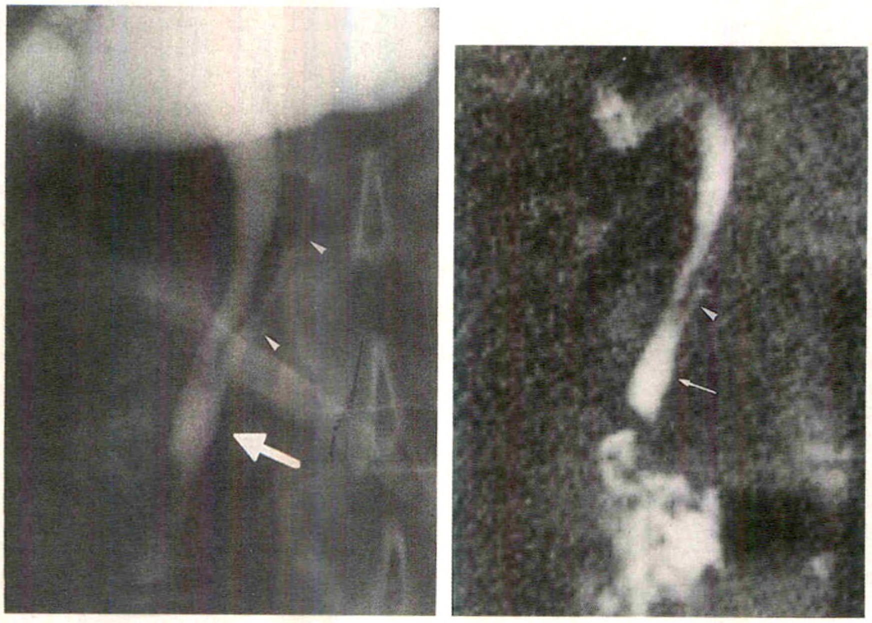

Fig. 3 Anomalous pancreaticobiliary junction without congenital choledochal cyst in a 35-year-old woman. **a** Endoscopic retrograde cholangiopancreatography shows a long common channel (arrow), a non-dilated common bile duct and the main pancreatic duct (arrowheads). **b** Magnetic resonance cholangiopancreatography shows a long common channel (arrow). The arrowhead indicates the main pancreatic duct

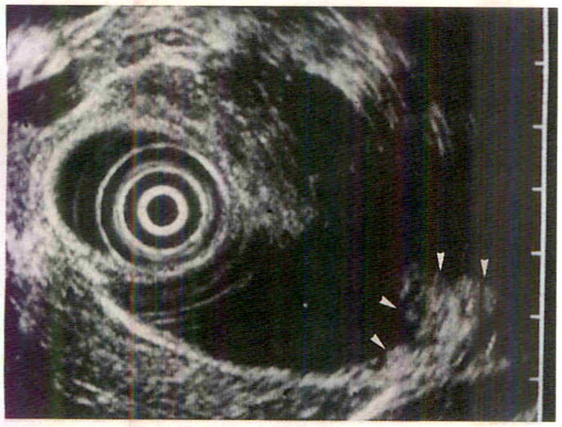

Fig. 4 Gallbladder carcinoma associated with anomalous pancreaticobiliary junction without congenital choledochal cyst in a 49-year-old man. Endoscopic ultrasonography shows a 34 × 20-mm hyperechoic sessile mass (arrowheads) in the gallbladder fundus. Histological examination of the surgical specimen revealed adenocarcinoma invading the subserosal layer of the gallbladder

common bile duct measured 5–14 (mean 9) mm. Endoscopic ultrasonography demonstrated a long common channel (12 mm or more) in nine of ten patients (*Fig. 2*) and a 5-mm channel in one. MRCP depicted a long common channel (12 mm or more) in all five patients examined with this modality (*Fig. 3b*). Ultrasonography failed to demonstrate a long common channel in any of the patients.

Ultrasonography and endoscopic ultrasonography detected and confirmed the diagnosis of all gallbladder carcinomas (*Table 1*). Carcinomas were demonstrated as a hyperechoic or hypoechoic sessile polyp (*Fig. 4*) or a large, irregularly surfaced, heterogeneously hypoechoic mass. In one patient with adenoma, ultrasonography and endoscopic ultrasonography demonstrated an 8-mm homogeneously hyperechoic, semipedunculated polyp but failed to distinguish it from carcinoma. Ultrasonography detected a cholesterol polyp in two patients but could not rule out carcinoma in one of the two. In this patient, however, endoscopic ultrasonography demonstrated aggregation of echogenic spots and accurately demonstrated the mass to be a cholesterol polyp. Mucosal hyperplasia was detected in ten of 11 patients by ultrasonography and in three of four by endoscopic ultrasonography. Ultrasonography and endoscopic ultrasonography showed a 1–5-mm symmetrical, diffuse, hypoechoic thickening of the inner mucosal layer of the gallbladder with an intact hyperechoic outer layer (*Fig. 1b*). Ultrasonography and endoscopic ultrasonography accurately detected the tumour in both patients with pancreatic carcinoma. MRCP failed to detect gallbladder lesions in all five patients examined with this modality.

The diagnosis of APBJ was established before operation in all 18 patients. In 14 symptomatic patients, polypoid lesions or mucosal thickening in the gallbladder, or pancreatic cancer, demonstrated by ultrasonography, led to further examination by ERCP, endoscopic ultrasonography or MRCP. APBJ was thereby diagnosed in all 14 patients. In four asymptomatic patients, gallbladder lesions that were detected incidentally by ultrasonography during regular checkups ($n = 3$) or pregnancy ($n = 1$) indicated a need for detailed examination. Subsequently, ERCP, endoscopic ultrasonography or MRCP confirmed APBJ.

Surgical treatment

All 18 patients were treated surgically. Of the eight patients with gallbladder carcinoma, five underwent extended cholecystectomy (excision of the gallbladder and its bed), excision of the extrahepatic bile duct, wide dissection of lymph nodes and Roux-en-Y hepaticojejunostomy. The other three patients received palliative cholecystectomy for well advanced carcinoma. Two patients with pancreatic carcinoma underwent pancreatic resection with cholecystectomy. Eight patients without malignant disease underwent cholecystectomy alone.

Of the eight patients with gallbladder carcinoma, only three are still alive 2·8–5 (mean 3·7) years after operation. Five patients died from carcinoma 3–30 (mean 14) months after operation. Both patients with pancreatic carcinoma died from recurrent disease, 8 months and 2 years after operation. All eight patients without malignancy have been alive and asymptomatic for a mean of 4·7 years (range 7 months to 7 years) since cholecystectomy. None of the 18 patients developed acute pancreatitis or bile duct carcinoma. One patient with bile duct excision experienced acute cholangitis which was managed conservatively.

Incidence of anomalous pancreaticobiliary junction and total number of gallbladder lesions

The review of ERCP records in 934 cases during the same period yielded 47 cases (5·0 per cent) of APBJ (29 with and 18 without CCC). All 47 patients underwent surgical treatment. Of the 29 patients with APBJ and CCC, four had gallbladder carcinoma, two had bile duct carcinoma and 13 had mucosal hyperplasia of the gallbladder. As well as 12 patients with gallbladder carcinoma and APBJ (four with and eight without CCC), 57 other patients without APBJ (mean age 57·1 years) were treated for gallbladder carcinoma during the same period. Of 625 patients without APBJ who underwent cholecystectomy, two (0·3 per cent) had severe mucosal hyperplasia of the gallbladder at histological examination.

Discussion

APBJ without CCC was found in 1·9 per cent of cases detected by ERCP in the present study. APBJ without CCC was associated with a high prevalence of gallbladder carcinoma (eight of 18 patients), which is consistent with the results of previous studies (33–73 per cent)[2,6,8,9]. Gallbladder carcinoma in patients with APBJ without CCC ($n = 8$) constituted 12 per cent of all patients with gallbladder cancer ($n = 69$) treated during the same period. The mean age of patients with gallbladder cancer and APBJ was lower, by approximately 10 years, than that of those without APBJ, as reported previously[2,8].

Gallbladders with mucosal hyperplasia showed a marked (1·2–5·1 mm), diffuse thickening of the mucosa, compared with the mucosal height (less than 0·6 mm)[17] of the normal gallbladder. The prevalence of mucosal hyperplasia was high (11 of 18 patients) in the present series, as in previously reported series of APBJ (39–64 per cent)[17,18]. In patients without APBJ, severe mucosal hyperplasia is observed only rarely: in 0·3 per cent (in the present study), 0·4 per cent[19] or 0·7 per cent[20]. Therefore, mucosal hyperplasia strongly suggests the presence of APBJ.

The aetiology of gallbladder carcinoma in APBJ without CCC has not been fully clarified. In patients with APBJ, gallstones do not appear to contribute to carcinogenesis, based on the low rate of gallstone detection (13–18 per cent in previously reported series[2,8]; one of eight patients in the present study), in contrast to patients without APBJ. APBJ allows reflux of pancreatic juice into the biliary tract, as reflected by the high amylase level in gallbladder bile in the present and previous studies[7]. Refluxed proteolytic pancreatic enzymes and phospholipase A_2 are activated in the biliary tract[21]. Phospholipase A_2, which has a direct proliferative effect on the gallbladder mucosa[18], produces lysophosphatidylcholine, which has a cytotoxic effect[21]. These agents may cause mucosal hyperplasia and carcinoma of the gallbladder. A sequence of hyperplasia, characterized by increased cellular kinetics, through dysplasia to carcinoma may be involved in the carcinogenesis that occurs in APBJ without CCC[17,18,22]. In the present study, 16 of 18 patients had mucosal hyperplasia, adenoma or carcinoma of the gallbladder. The present series included two pancreatic carcinomas. Only a few pancreatic cancer cases with APBJ have been reported[23]. The relationship between these two diseases thus remains unclear.

In the present study, five of the 18 patients developed acute pancreatitis. The incidence is reportedly 44–68 per cent in APBJ[4,6,24]. Although the hydropressure within the pancreatic duct is usually greater than in the bile duct[25], bile may reflux into the pancreatic duct via the anomalous junction in some situations, such as postprandial gallbladder emptying. This reflux may contribute to acute pancreatitis. All three patients with a history of previous episodes of acute pancreatitis had no further attacks after cholecystectomy alone.

In the present study, endoscopic ultrasonography (90 per cent) and MRCP (100 per cent) were almost as sensitive as ERCP (100 per cent) in the detection of APBJ although only five patients had MRCP. Both imaging techniques are less invasive than ERCP. Furthermore, endoscopic ultrasonography allows accurate differentiation of polypoid lesions in the gallbladder (carcinoma *versus* cholesterol polyps)[12,13], which facilitated the planning of operative procedures. MRCP failed to depict gallbladder lesions. However, MRCP is neither operator-dependent nor associated with any discomfort for patients, in contrast to ERCP and endoscopic ultrasonography. Therefore, endoscopic ultrasonography and MRCP are potentially useful alternatives to ERCP for diagnosing APBJ[13,26].

Clues to the diagnosis of APBJ without CCC have not been described. Of the present 18 patients, 14 had symptoms. Screening with ultrasonography detected pancreatobiliary abnormalities in all patients. With the exception of the two patients with pancreatic carcinoma, all gallbladders showed diffuse mucosal hypoechoic thickening (hyperplasia) and/or polypoid lesions (carcinoma or adenoma) on ultrasonography. Polypoid lesions suggest adenoma or carcinoma, if ultrasonography does not show characteristic features of cholesterol polyps (usually less than 10 mm in diameter, pedunculated, and with a single tiny echogenic spot or an aggregation of echogenic spots) or adenomyomatosis (multiple intramural cysts)[12]. Suspected adenomas or carcinomas require further examination with endoscopic ultrasonography or ERCP for differentiation and staging, and to ascertain the presence of APBJ[12,13]. Accordingly, polypoid gallbladder lesions or diffuse hypoechoic thickening of the gallbladder mucosa demonstrated on ultrasonography, or acute pancreatitis of unknown aetiology, should prompt further investigation to screen for APBJ.

The treatment of choice for APBJ with CCC is excision of the extrahepatic bile duct and gallbladder with Roux-en-Y reconstruction of the biliary tree[3]. However, a standard treatment protocol for APBJ without CCC has not been established. Gallbladder carcinoma associated with APBJ should be treated utilizing the procedure for gallbladder carcinoma without APBJ. These carcinomas require cholecystectomy, resection of the liver (gallbladder bed resection or major hepatectomy), extrahepatic bile duct excision and wide dissection of lymph nodes, based on the tumour stage[27].

For patients with APBJ without CCC but with no cancer, the authors recommend prophylactic cholecystectomy because of the high possibility of gallbladder carcinoma developing in the future. However, excision of the extrahepatic bile duct is unnecessary because bile duct carcinomas rarely develop in patients with APBJ without CCC[5]. In the present study, no bile duct carcinomas developed after cholecystectomy not involving resection of the APBJ. No patient experienced either acute pancreatitis or acute cholangitis after operation. On the other hand, Lilly *et al.*[28] advocated excision of the extrahepatic bile duct, particularly for symptomatic patients. However, they reported a high (50 per cent) incidence of postoperative recurrent cholangitis. Reconstruction of the non-dilated biliary tree carries a risk of postoperative stricture and recurrent cholangitis. Nevertheless, meticulous pathological examination of the gallbladder and careful follow-up are necessary for patients treated with cholecystectomy alone.

In conclusion, APBJ without CCC is a high-risk condition for the development of gallbladder carcinoma. Prophylactic cholecystectomy before carcinoma develops is recommended. For early diagnosis of APBJ, gallbladder abnormalities on ultrasonography (polypoid lesions or diffuse hypoechoic thickening of the mucosal layer), or acute pancreatitis of unknown aetiology, should prompt further investigation with ERCP or less invasive imaging modalities, such as endoscopic ultrasonography and MRCP.

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Follow-up of more than 10 years after endoscopic sphincterotomy for choledocholithiasis in young patients

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Background With the advent of laparoscopic cholecystectomy, the indications for endoscopic sphincterotomy (ES) have been extended to young patients with choledocholithiasis. However, the long-term results of ES are largely unknown.

Methods Between 1977 and 1986, 115 patients aged 60 years or less underwent ES for choledocholithiasis. Stone classification, and early and long-term outcomes of ES were analysed retrospectively.

Results Early complications occurred in nine patients (7·8 per cent), but there were no deaths. ES and stone clearance were successful in 110 patients. Long-term information was available in 103 of the 110 patients, with a mean overall follow-up duration of 14·2 (range 10·4–19·3) years. Ten patients (9·7 per cent) developed late complications, including stone recurrence and/or cholangitis (nine patients) and acute cholecystitis (one of 23 patients with the gallbladder *in situ*). The choledochal complication rate was somewhat higher in patients with calcium bilirubinate stones at ES (seven of 65 patients) than in those with cholesterol stones (two of 38 patients). Choledochal complications were manageable endoscopically.

Conclusion Approximately 10 per cent of patients develop late complications. However, endoscopic retreatment is safe and effective. ES is a reasonable method for treating choledocholithiasis, even in young patients.

Young patients do not develop common bile duct stones as often as elderly patients. However, the treatment strategy selected for choledocholithiasis in young patients is an important issue to be resolved in the era of laparoscopic cholecystectomy[1]. Treatment options include endoscopic sphincterotomy (ES), laparoscopic surgery (transcystic stone retrieval or direct choledochotomy) and open bile duct exploration[1]. ES is a widely accepted method of extracting common bile duct stones in elderly or high-risk patients and in those with severe cholangitis or pancreatitis[2–4]. ES is associated with potential long-term complications, such as biliary pain, stone recurrence and cholangitis, secondary to sphincter ablation or papillary stenosis. However, the risks of developing such late complications are negligible in elderly, and even many high-risk, patients because of their relatively short life expectancies. Recently, the indications for ES have been extended to young patients with few, if any, non-biliary disorders, in association with the advent of laparoscopic cholecystectomy[5–7]. Combined use of laparoscopic cholecystectomy and preoperative or postoperative ES is a minimally invasive and relatively convenient treatment for co-existing gallbladder and ductal stones. However, this emerging indication of ES is still controversial because little information is available on the long-term (10 years or more) outcome of ES[8,9], particularly in young patients.

To evaluate the role of ES for choledocholithiasis in young patients, the present retrospective study analysed clinical features of young patients (aged 60 years or less) who underwent ES for choledocholithiasis, as well as the short-term and long-term (10 years or more) results of ES. Furthermore, the relation of stone classification and long-term outcome was analysed.

Patients and methods

Between 1977 and 1986, a total of 382 patients underwent ES for choledocholithiasis at this hospital and two affiliated hospitals. Patients with concomitant hepatolithiasis or bile duct stricture were excluded from the study. Among these patients, 115 (30·1 per cent) were 60 years or younger at the time of the initial endoscopic procedure. There were 54 men and 61 women with a mean age of 50 (range 21–60) years.

ES was usually performed to the upper margin of the papillary roof, using side-view duodenoscopes and standard pull-sphincterotomes. Stone extraction with a basket or balloon catheter was attempted routinely during the initial endoscopic procedure.

Clinical features, stone classifications, and early and long-term outcomes of ES were analysed in these young patients. Gallstones were classified as cholesterol, calcium bilirubinate or black stones, according to the cross-sectional findings[10]. Cholesterol stones showed a radial pattern with a white to light yellow colour. Calcium bilirubinate stones (brown pigment stones) had multiple concentric layers with a brown colour. These stones are common in Japanese patients, particularly those with primary common bile duct stones. Black stones were dark brown or black, friable and amorphous. These stones contain mainly unconjugated bilirubin and are called pigment stones in the USA and Europe. Early complications (within 30 days of ES) were classified according to the 1991 consensus guidelines[11].

Long-term follow-up data were obtained from medical charts at the authors' outpatient clinic or from the patients, their families and/or their local practitioners by mail and/or telephone, in March 1997. Accordingly, the minimum overall duration of follow-up was 10 years. The data included (1) biliary symptoms (abdominal pain, jaundice, fever and chills), (2) medical investigation (liver function tests and imaging studies) if performed, (3) medical and surgical treatment, and (4) causes of death, since the first ES. If symptoms, liver function tests or abdominal ultrasonography indicated possible biliary pathology, patients were advised to undergo repeat endoscopic retrograde cholangiopancreatography (ERCP).

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Results were analysed by means of Fisher's exact probability test. Differences were considered significant at a P value of less than 0·05. The probability of biliary complications occurring during follow-up was determined using the Kaplan–Meier method.

Results

Among the 115 young patients who underwent ES for choledocholithiasis, 66 had previously undergone cholecystectomy, with ($n = 40$) or without ($n = 26$) bile duct exploration. The interval between primary surgery and ES ranged from 6 days to 11 years (mean 15 months). Eight patients underwent ES within 30 days of cholecystectomy without bile duct exploration. Six patients had undergone two operations for bile duct stones. At ES, 49 patients had *in situ* gallbladders; 36 had gallbladder stones and 13 did not. Of the 115 patients, 36 presented with acute cholangitis and 15 with gallstone pancreatitis. Thirteen patients had concomitant medical problems, including liver cirrhosis ($n = 5$), recent myocardial infarction ($n = 2$), chronic renal failure ($n = 2$), diabetes ($n = 2$), chronic obstructive pulmonary disease ($n = 1$) and congestive heart failure ($n = 1$). ES was performed on an emergency basis in 40 patients with acute cholangitis ($n = 27$) or acute pancreatitis ($n = 13$).

ES was successful in 112 (97·4 per cent) of 115 patients but failed in three patients with gallbladder and bile duct stones. At ERCP, the intrahepatic bile ducts showed no abnormalities. Stenosis of the extrahepatic bile duct or papillary orifice was not found. Bile duct clearance was achieved in 110 patients (95·7 per cent), after one endoscopic procedure in 91 patients and after two or more procedures in 19. The remaining two patients with previous choledochal exploration underwent surgical treatment for retained bile duct stones.

Early complications (within 30 days of ES) occurred in nine patients (7·8 per cent), and included bleeding and acute pancreatitis (*Table 1*). One perforation necessitated emergency surgery. The eight remaining complications were mild and all were managed medically. No ES-related deaths occurred. Only one of the 13 patients with concurrent medical problems experienced an ES-related complication (mild acute pancreatitis).

Table 1 Early complications after endoscopic sphincterotomy in 115 patients

	No. of patients	Required operation
Acute pancreatitis	4 (3·5)	0
Haemorrhage	3 (2·6)	0
Perforation	1 (0·9)	1
Acute cholangitis	1 (0·9)	0
Total	9 (7·8)	1

Values in parentheses are percentages

Of 33 patients with gallbladder stones at the time of ES, 23 underwent elective cholecystectomy 5–37 (mean 10) days after successful ES. The gallbladder was left *in situ* after ES in 23 patients with ($n = 10$) or without ($n = 13$) cholelithiasis.

Patients with previous cholecystectomy had a high prevalence of calcium bilirubinate stones in calculi extracted at ES (*Table 2*). However, all eight patients with recent (30 days or less) cholecystectomy had cholesterol stones, which were considered to be residual at the time of surgery. Among those with gallbladder *in situ*, most patients with gallbladder stones had cholesterol stones but all patients without gallbladder stones had calcium bilirubinate stones. None of the present patients had black stones.

Long-term outcome

Long-term information was available in 103 (93·6 per cent) of 110 patients with successful ES and bile duct clearance. The overall duration of follow-up ranged from 10·4 to 19·3 (mean 14·2) years. Seven patients (6·4 per cent) were lost to follow-up. During the follow-up period, 16 patients died from non-biliary disease 6·5–17·3 (mean 12·0) years after ES. There were no deaths related to biliary disease.

Of the 103 patients, ten (9·7 per cent) experienced biliary symptoms during follow-up (*Table 3*). Five patients developed acute cholangitis 1·7–11·0 (mean 5·3) years after ES. In these five patients, repeat ERCP revealed recurrent bile duct stones with papillary stenosis in three,

Table 2 Classification of common bile duct stones extracted at endoscopic sphincterotomy in 110 patients

	n	Cholesterol stone	Calcium bilirubinate stone
After cholecystectomy			
With choledochal exploration	38	4	34
Without choledochal exploration	26	12	14
Gallbladder *in situ*			
With cholelithiasis	33	25	8
Without cholelithiasis	13	0	13
Total	110	41	69

Table 3 Long-term follow-up after endoscopic sphincterotomy by stone classification at the initial endoscopic sphincterotomy in 110 patients with complete ductal clearance

		Symptomatic				
Stone classification	n	Acute cholangitis	CBD stone recurrence	Acute cholecystitis	Asymptomatic	Lost to follow-up
Cholesterol stone	41	1	1	1	35	3
Calcium bilirubinate stone	69	4	3	0	58	4
Total	110	5	4	1	93	7

CBD, common bile duct

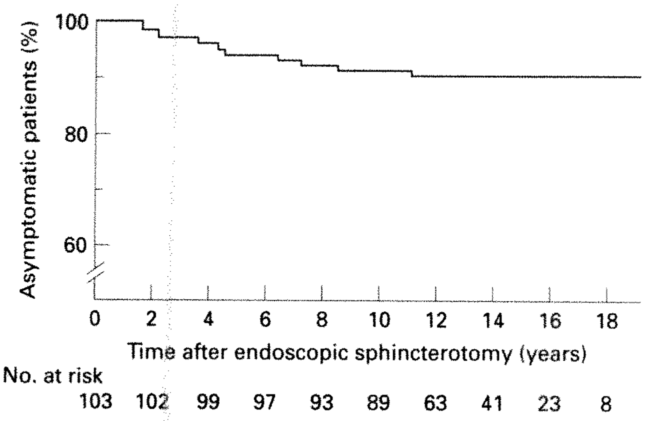

Fig. 1 Kaplan–Meier plot for the absence of late complications in 103 patients who underwent successful endoscopic sphincterotomy, achieving ductal clearance

bile duct stones alone in one and papillary stenosis alone in one. Another four patients presented with obstructive jaundice and/or biliary pain 2·3–7·3 (mean 5·2) years after ES. ERCP showed recurrent choledocholithiasis with ($n = 3$) or without ($n = 1$) papillary stenosis. In the seven patients with papillary stenosis, the initial ES had been performed to the upper margin of the papillary roof (a large incision; $n = 5$) or to below the upper margin (a middle incision; $n = 2$). Only one of the seven patients had experienced an early complication (mild pancreatitis) after ES. Of the 23 patients with the gallbladder *in situ*, one with gallbladder stones developed acute cholecystitis 2·3 years after ES, which necessitated cholecystectomy. In this patient, repeat ERCP detected no abnormalities in the common bile duct. No cases of liver abscess or biliary malignancy were recorded after ES.

The eight patients with recurrent choledocholithiasis underwent successful transpapillary stone extraction, combined with repeat ES in six. All eight had calcium bilirubinate stones at recurrence. One patient with acute cholangitis without bile duct stones underwent ES. Neither early nor long-term complications occurred after endoscopic retreatment in these nine patients.

Ninety-three patients were free from biliary symptoms as of March 1997 or until death. During follow-up, 19 patients underwent repeat ERCP, mostly because of mild cholestatic liver dysfunction or suspected bile duct stones on ultrasonography; seven of the 19 patients underwent ERCP in 1997. However, none of these patients had evidence of recurrent choledocholithiasis or papillary stenosis on ERCP.

Excluding one case of acute cholecystitis, biliary complications occurred in two of 38 patients with cholesterol stones and in seven (11 per cent) of 65 with calcium bilirubinate stones at the initial ES; the difference was not significant ($P = 0·28$) (*Table 3*). The cumulative incidence of late complications was 9 per cent at 10 years and 10 per cent at 15 years (*Fig. 1*). Most complications occurred during the first 10 years.

Discussion

In the present study, young patients underwent ES mainly for recurrent bile duct stones after cholecystectomy or for acute complications of choledocholithiasis, including acute cholangitis and acute pancreatitis. The majority of young patients had no surgical risks due to concurrent medical problems, in contrast to elderly patients. However, 4·3 per cent of the present patients had liver cirrhosis. Surgical treatment of choledocholithiasis in such patients has been reported to carry an extremely high risk[12]. In the present series, patients with cirrhosis underwent ES successfully and safely.

In the present study, the success rate was 97·4 per cent for ES and 95·7 per cent for stone extraction. The early complication rate after ES was 7·8 per cent with no deaths. Most of the complications were mild and could be managed medically, the exception being one case of a perforation which occurred early in the authors' experience. A previous study collected a large amount of data on early complications of ES[11]. Overall morbidity and mortality rates were reported to be 7–11 per cent and 0–2 per cent respectively[11]. The ES complication rate depends on technical factors rather than concurrent medical risk factors[2,13]. Accordingly, ES carries a risk for early complications even in young patients. The results of the present study were, however, acceptable in young, otherwise healthy patients.

In the present study, a relatively small number of patients (6·4 per cent) was lost to follow-up. All patients with biliary symptoms underwent repeat ERCP. Furthermore, most asymptomatic patients with mild cholestatic liver dysfunction or suspected bile duct stones on ultrasonography underwent ERCP. Therefore, the true late complication rate after ES could be calculated. The incidence of biliary complications during the mean follow-up period of 14·2 years was 9·7 per cent. Almost all complications occurred within 10 years of ES. Most of the late complications were recurrent bile duct stones and acute cholangitis, the incidence being 8·7 per cent. No biliary malignancies developed after ES. In the literature late biliary complications after ES have occurred in 5·8–18 per cent of patients during a mean follow-up of less than 8 years (*Table 4*). However, only a few reports have described the late complication rate (5·8 per cent[9] and 24 per cent[8]) for a mean follow-up exceeding 10 years. The present figure (9·7 per cent) takes an intermediate position between the two previously reported results. The present data compare favourably with the results obtained by surgical duct re-exploration for recurrent stones (a complication rate of 18–33 per cent after 5–10 years of follow-up[21,22]). However, the literature concerning long-term outcomes after primary surgery for bile duct stones, particularly cholesterol stones (secondary stones), is scarce. Furthermore, long-term results after laparoscopic surgery for choledocholithiasis have not been reported.

In the present series, seven of nine late choledochal complications were associated with papillary stenosis. An inadequate incision and a bleeding sphincterotomy requiring a sclerosing injection have been reported to be potential risk factors for papillary stenosis[9,19]. However, the present study could not confirm the theory. All recurrent stones were calcium bilirubinate stones, which are generally considered to result from bacterial infection[10,23]. Bactobilia, bile stasis and papillary stenosis may play important roles in the pathogenesis of recurrent stones[24,25]. Calcium bilirubinate stones are often found in cases of primary bile duct stones or recurrent stones[10]. Such patients require careful follow-up after ES. Late complications were managed safely and successfully with ERCP.

Table 4 Summary of published data concerning follow-up after endoscopic sphincterotomy for choledocholithiasis

Reference	Year	No. of patients with follow-up	Mean (range) follow-up (years)	Late complications (%)
Rösch *et al.*[14]	1981	248	— (0·5–7)	12·9
Riemann *et al.*[15]	1983	340	4·5 (2–9)	18
Jacobsen and Matzen[16]	1987	52	6 (0·7–8·6)	8
Ikeda *et al.*[17]	1988	408	3·7 (0·5–10·5)	5·8
Davidson *et al.*[18]	1988	85	2·5 (1–8)	9·4
Hawes *et al.*[19]	1990	115	8 (6·5–11)	13
Testoni and Tittobello[20]	1991	96	4 (2–8)	15
Prat *et al.*[9]	1996	154	11 (8·5–13)	5·8
Bergman *et al.*[8]	1996	94	14 (3–18)	24
Present study	1998	103	14·2 (10·4–19·3)	9·7

Acute cholecystitis developed after ES in one of ten patients with gallbladder calculi but in none of 13 patients with an acalculous gallbladder. ES had previously been considered to increase the risk of acute cholecystitis. However, recent reports have demonstrated a low incidence of cholecystitis after ES, particularly in patients with an acalculous gallbladder[26,27]. The authors have shown that ES actually improves gallbladder motility somewhat[27]. Prophylactic cholecystectomy for an acalculous gallbladder may be unnecessary even for young, essentially healthy, patients.

In treating common bile duct stones, ES is basically safe but does carry a risk of early complications. Even in young patients, ES should be performed by skilful endoscopists. Approximately 10 per cent of patients develop late complications such as stone recurrence or acute cholangitis, mostly within 10 years of ES. Careful follow-up after ES is necessary, particularly for patients with calcium bilirubinate stones at ES. Although the late complication rate after ES is not negligible, retreatment with ERCP is safe and effective. ES is a reasonable method for treating choledocholithiasis, even in young patients.

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Postoperative weight gain after standard Whipple's procedure *versus* pylorus-preserving pancreatoduodenectomy: the influence of tumour status

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Background Recent reports suggest a better postoperative weight gain after pylorus-preserving pancreatoduodenectomy (PPPD) compared with standard pancreatoduodenectomy (PD). Factors that could also influence postoperative weight gain, such as tumour-positive resection margins and tumour recurrence, have not been taken into account in these studies. The aim of this prospective study was to evaluate weight gain in the first 15 months after PD or PPPD and to investigate the influence of other tumour-related factors.

Methods From 1991 to 1995, 140 patients underwent subtotal pancreatoduodenectomy; 125 patients underwent resection for malignant disease of the pancreatic head region (56 had PD and 69 PPPD). Patients' weights were evaluated in the pre-illness phase, before operation and during four postoperative phases (at 3, 7, 11 and 15 months). Weight was calculated as a percentage of the pre-illness weight. Patients were subdivided according to tumour status: PD with positive and PD with negative tumour status; PPPD with positive and PPPD with negative tumour status. Tumour-positive status was defined as either microscopically tumour-positive resection margins or radiologically or cytologically proven tumour recurrence within 2 years of surgery.

Results Five patients died during the hospital stay (PD, four; PPPD, one) (overall mortality rate 4 per cent). There was no difference in overall weight gain between patients having PD and PPPD. There was, however, a difference in patients with positive and negative tumour status for PD ($P = 0.0003$) and PPPD ($P < 0.0001$).

Conclusion There is only a minimal difference in postoperative weight gain between patients having PD and PPPD. Differences in postoperative weight gain are related more to positive resection margins and tumour recurrence than to the type of resection.

Pancreatoduodenectomy is a major surgical procedure which is accompanied by a mortality rate of less than 5 per cent in specialized centres[1–6]. This procedure still has a significant morbidity rate of up to 60 per cent[2,3,5–8]. After the introduction of pylorus-preserving pancreatoduodenectomy (PPPD), early studies suggested that postoperative gastric emptying was delayed[9–12]. This has not been confirmed in recent reports[13–15] and the PPPD is thought to have advantages over the standard Whipple procedure. The procedure is less time consuming and has been reported to be associated with less intraoperative blood loss[13,14,16]. PPPD is now accepted in most centres as the favoured reconstruction after pancreatic head resection.

Another important advantage of PPPD is better postoperative weight gain compared with that following standard Whipple resection, as reported in a number of retrospective studies[13,14,17]. In these studies postoperative weight gain was usually assessed only at one time point in the postoperative period. After pylorus-preserving resection more patients were reported to gain weight in the postoperative period than following standard Whipple resection, but the exact time point of postoperative weight assessment and the number of weight measurements were not stated[14]. Zerbi *et al.*[13] assessed weight gain as a percentage of pre-illness weight and demonstrated an advantage for patients after pylorus-preserving resection at 6 months after operation[13]. It is, however, remarkable that tumour recurrence after resection was not taken into account in these studies. Tumour recurrence is probably an important factor in determining weight gain.

From 1993, the preferred surgical reconstruction in the authors' department changed gradually from the standard Whipple procedure towards the pylorus-preserving resection. In this study a consecutive series of patients undergoing pancreatoduodenectomy for malignant disease of the pancreatic head region was evaluated prospectively to determine whether the pylorus-preserving procedure resulted in improved weight gain in the first postoperative year compared with the standard Whipple resection. The influence of microscopically tumour-positive resection margins and tumour recurrence on weight gain was taken into account in the analysis.

Patients and methods

From 1991 to 1995, 140 consecutive patients underwent subtotal pancreatoduodenectomy. Fifteen patients had benign disease on

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histopathological examination of the resection specimen and were therefore excluded from the study, leaving 125 patients who underwent resection for malignant disease of the pancreatic head region. Fifty-six patients were treated with a standard Whipple resection and 69 underwent PPPD. Before January 1993 only standard Whipple's resections were performed. In the following period a gradual preference for the pylorus-preserving procedure developed. Other changes in the surgical protocol that were introduced in 1993 were: reconstruction with one jejunal loop for the pancreatic, biliary and gastric anastomosis instead of a separate Roux-en-Y loop for the pancreatic and biliary anastomosis; the pancreaticojejunal anastomosis was performed in one running layer instead of two layers. Furthermore, transluminal drainage of the pancreatic duct was performed only in the earlier period, before 1993.

All data concerning preoperative evaluation, intraoperative parameters, and postoperative morbidity and mortality were collected prospectively. Both groups were compared with respect to age, sex, preoperative bilirubin (μmol/l) and albumin (g/l) levels, operating time, blood loss and transfusions, histopathological diagnosis, microscopic radicality of the resection, postoperative morbidity and mortality. Morbidity was defined as any postoperative complication requiring medical or surgical intervention, causing prolonged hospital stay, readmission to the intensive care unit or leading to postoperative death. Mortality was defined as death during hospital stay.

Pancreatic endocrine and exocrine function were compared in these two groups. Pancreatic endocrine insufficiency was defined as glucose intolerance necessitating oral medication or insulin administration. Pancreatic exocrine insufficiency was defined as fat intolerance, requiring pancreatic exocrine supplementation during outpatient treatment, which improved with pancreatic enzyme treatment. Patients receiving postoperative radiotherapy and chemotherapy were identified in both groups. (A number of patients received additional radiotherapy or chemotherapy in a randomized multicentre trial (European Organisation for Research on Treatment of Cancer)).

Weight assessment

Preoperative and postoperative weights were computed as a percentage of the pre-illness weight, as inquired at the preoperative assessment. Postoperative weights were measured prospectively in the outpatient clinic and divided into four successive postoperative phases: 3 ± 1, 7 ± 1, 11 ± 1 and 15 ± 1 months after operation.

Positive tumour status

Patients were divided into those with positive and negative tumour status. Patients with positive tumour status were defined as having microscopically non-radical resection margins or postoperative tumour recurrence during the first 2 years of follow-up. Tumour recurrence was defined as radiologically or cytologically proven tumour recurrence within 2 years after surgery. A microscopically radical resection was defined as both tumour-free resection margins and dissection margins of the resection specimen on histopathological examination. All patients had macroscopically radical resections, as this is a major requirement for performing pancreatoduodenectomy at this centre.

Thus, there were four groups: patients who had undergone a standard Whipple procedure with negative tumour status, patients who had a standard Whipple procedure with positive tumour status, patients who had a pylorus-preserving resection with positive tumour status and those who had PPPD with negative tumour status.

Statistical analysis

Weight was calculated as the mean(s.e.m.) percentage of pre-illness weight. Statistical analysis was performed with χ^2 analysis, the two-tailed Fisher's exact test and the Mann–Whitney *U* test, as applicable. $P < 0{\cdot}05$ was considered statistically significant.

Results

Eighty-two per cent of the standard Whipple resections were performed before July 1993, whereas 90 per cent of the pylorus-preserving resections were performed after July 1993. There were no differences in patients' characteristics, preoperative weight loss, plasma bilirubin and albumin levels (*Table 1*). Duration of the standard Whipple resection was significantly longer than that of PPPD: 6·4 *versus* 4·8 h. Blood loss and transfusion need were higher in patients who had a standard Whipple resection. There were no differences in histopathological diagnosis, microscopic radicality of the resection or postoperative morbidity. The overall morbidity rate for standard Whipple's resection and PPPD was 50 and 42 per cent respectively. The overall mortality rate was 4 per cent with no difference between the two groups.

Follow-up data were available for 49 of 56 patients after standard Whipple's resection (postoperative death, four; lost to follow-up, three). Sixty-six of 69 patients could be analysed after PPPD (postoperative death, one; lost to follow-up, two). Tumour recurrence was detected

Table 1 Period of resection, patient characteristics, intraoperative factors, pathology, and postoperative morbidity and mortality for 125 patients who underwent operation from January 1991 to November 1995 for malignant disease of the pancreatic head area

	PD ($n = 56$)	PPPD ($n = 69$)
Period of resection		
January 1991 to June 1993	46 (82)	7 (10)*
July 1993 to November 1995	10 (18)	62 (90)
Patient characteristics and preoperative factors		
Median (range) age (years)	62 (37–79)	65 (37–78)
Sex ratio (M:F)	30:26	29:40
Median (range) bilirubin (μmol/l)	19 (5–231)	16 (4–189)
Median (range) albumin (g/l)	43 (21–57)	45 (22–54)
Intraoperative parameters		
Median (range) operating time (h)	6·4 (3·5–10·3)	4·8 (2·5–8·5)†
Median (range) blood loss (ml)	1500 (300–7000)	1100 (300–4000)‡
Median (range) transfusion (units PRBCs)	3 (0–8)	2 (0–7)‡
Histopathological diagnosis		
Pancreatic head carcinoma	26 (46)	34 (49)
Distal bile duct carcinoma	6 (11)	11 (16)
Ampullary carcinoma	19 (34)	21 (30)
Other malignancy	5 (9)	3 (4)
Resection margin		
Radical (tumour free)	33 (59)	44 (64)
Non-radical	23 (41)	25 (36)
Postoperative morbidity and mortality		
Overall morbidity	28 (50)	29 (42)
Mortality	4 (7)	1 (1)

Values in parentheses are percentages unless otherwise stated. PD, standard Whipple resection; PPPD, pylorus-preserving pancreatoduodenectomy; PRBCs, packed red blood cells. *$P < 0{\cdot}0001$ *versus* PD (χ^2 analysis); †$P < 0{\cdot}0001$, ‡$P = 0{\cdot}02$ *versus* PD (Mann–Whitney *U* test) during the study period in 28 patients after standard Whipple resection and in 31 after PPPD (57 *versus* 47 per cent respectively, $P = 0\cdot28$). Furthermore, six patients with a non-radical Whipple resection did not show signs of tumour recurrence and therefore 34 were classified as having a positive tumour status after standard Whipple resection. Six patients showed no signs of tumour recurrence after a non-radical pylorus-preserving resection, and therefore 37 patients in this group were classified as having a positive tumour status. Similar numbers of patients had complete follow-up in both groups. Median follow-up (including patients who died during follow-up) was 17 and 18 months for standard and pylorus-preserving resection respectively ($P = 0\cdot20$). The number of patients receiving postoperative radiotherapy or chemotherapy was no different for each procedure (*Table 2*).

Patients had a higher incidence of clinical pancreatic exocrine insufficiency after standard Whipple resection compared with PPPD: 73 and 56 per cent respectively. This, however, was not statistically significant ($P = 0\cdot06$). There was no difference in the incidence of pancreatic endocrine insufficiency between the two groups (*Table 3*).

Table 2 Tumour recurrence, median follow-up and additional treatment in 115 patients* who underwent operation for malignant disease of the pancreatic head area

	PD ($n = 49$)	PPPD ($n = 66$)	P
Tumour recurrence			
Yes	28 (57)	31 (47)	0·28§
No	21 (43)	35 (53)	
Tumour status†			
Positive	34 (69)	37 (56)	0·15§
Negative	15 (31)	29 (44)	
No. of patients with complete follow-up‡	45 (92)	60 (91)	1·00#
Median (range) follow-up (months)	17 (2–63)	18 (3–36)	0·20¶
Additional treatment			
Radiotherapy	15 (31)	18 (27)	0·70§
Chemotherapy	7 (14)	16 (24)	0·19§

Values in parentheses are percentages. PD, standard Whipple resection; PPPD, pylorus-preserving pancreatoduodenectomy. *Of the initial study group ($n = 125$), five patients died after operation (PD, four; PPPD, one) and five were lost during follow-up (PD, three; PPPD, two). †Positive tumour status was defined as tumour recurrence within 2 years of follow-up, microscopically non-radical resection or both. ‡Defined as follow-up until 24 months or death. §χ^2 analysis; #two-tailed Fisher's exact test; ¶Mann–Whitney U test

Table 3 Pancreatic exocrine and endocrine function during the first year of follow-up in 115 patients who underwent operation for malignant disease of the pancreatic head area

	PD ($n = 49$)	PPPD ($n = 66$)	P*
Exocrine insufficiency	36 (73)	37 (56)	0·06
Endocrine insufficiency	10 (20)	17 (26)	0·45
Sufficient endocrine or exocrine function	11 (22)	24 (36)	0·11

Values in parentheses are percentages. PD, standard Whipple resection; PPPD, pylorus-preserving pancreatoduodenectomy. *χ^2 test

Postoperative weight

Preoperative weight and weight 3 months after operation was no different between the standard Whipple resection and the pylorus-preserving resection. Weight at 7, 11 and 15 months after operation was not significantly different between the two surgical procedures (*Fig. 1*).

Patients with negative tumour status ($n = 44$) had a postoperative weight gain from a mean(s.e.m.) of 87(1·3) per cent at 3 months to 94(1·7) per cent of pre-illness weight at 15 months after operation. Patients with positive tumour status ($n = 71$) had an overall weight loss from 86(1·0) to 81(2·2) per cent of pre-illness weight in the same period (*Fig. 2*).

There were no differences in mean weight among the four subgroups on admission and at 3 months after operation. There was no difference in weight gain between the two procedures, in patients with negative tumour status or in those with positive tumour status within 15 months of operation (*Fig. 3*).

Total weight gain from 3 to 15 months after operation was no different between the standard Whipple procedure

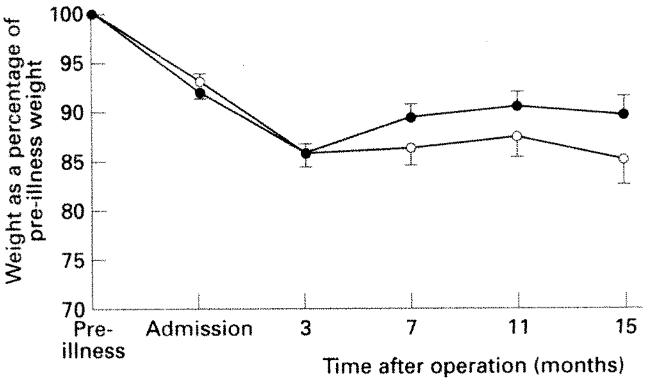

Fig. 1 Postoperative weight change as a percentage of pre-illness weight for all patients who underwent pancreatoduodenectomy for malignant disease of the pancreatic head region ($n = 115$): ○, standard Whipple procedure ($n = 49$); ●, pylorus-preserving pancreatoduodenectomy ($n = 66$). Values are mean(s.e.m.). Not significantly different at any time point

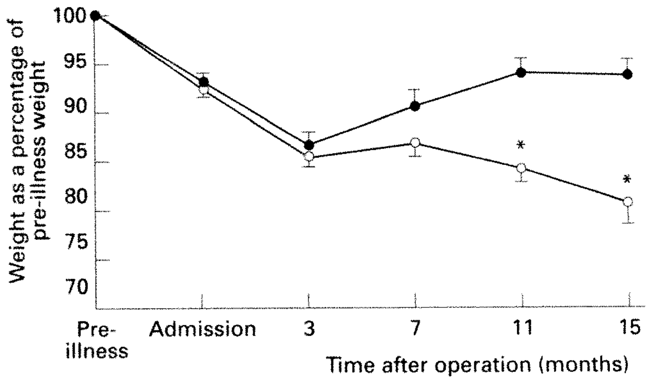

Fig. 2 Postoperative weight change as a percentage of pre-illness weight for patients who underwent pancreatoduodenectomy for malignant disease of the pancreatic head region ($n = 115$). ○, Patients with positive tumour status during follow-up ($n = 71$); ●, patients with negative tumour status ($n = 44$). Values are mean(s.e.m.). *$P < 0\cdot0001$ (Mann–Whitney U test)

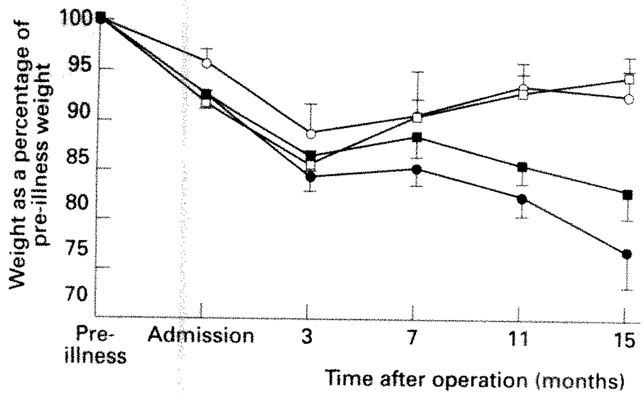

Fig. 3 Postoperative weight change as a percentage of pre-illness weight for the four groups of patients who underwent pancreatoduodenectomy for malignant disease of the pancreatic head region ($n = 115$). ○, Standard Whipple procedure, negative tumour status ($n = 15$); ●, standard Whipple procedure, positive tumour status ($n = 34$); □, pylorus-preserving pancreatoduodenectomy (PPPD), negative tumour status ($n = 29$); ■, PPPD, positive tumour status ($n = 37$). Values are mean(s.e.m.). There were no significant differences between procedures for patients with positive or negative tumour status

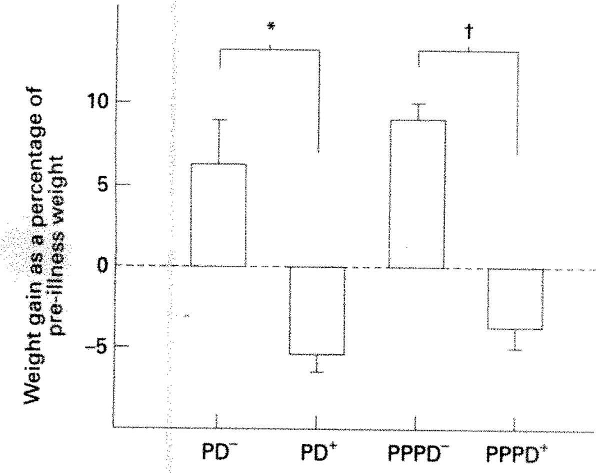

Fig. 4 Total weight gain (as a percentage of pre-illness weight) between 3 and 15 months after operation for the four different groups of patients who underwent pancreatoduodenectomy for malignant disease of the pancreatic head region ($n = 115$). PD$^-$, standard Whipple procedure, negative tumour status; PD$^+$, PD with positive tumour status; PPPD$^-$, pylorus-preserving pancreatoduodenectomy, negative tumour status; PPPD$^+$, PPPD with positive tumour status. Values are mean(s.e.m.). $^*P = 0{\cdot}0003$, $^\dagger P < 0{\cdot}0001$ (Mann–Whitney U test)

and PPPD, both in patients with negative tumour status and in those with positive tumour status. Patients with negative tumour status had a significantly better weight gain between 3 and 15 months after operation compared with those with a positive tumour status, after both types of resection (*Fig. 4*).

Discussion

In previous studies on weight gain after pancreatoduodenectomy, tumour-related factors such as the influence of non-radical resection or tumour recurrence were not evaluated[13,14,17]. In the present study tumour recurrence was defined as clinically evident tumour recurrence within 2 years of surgery. The authors are aware that a few more patients will eventually develop tumour recurrence during further follow-up. This will, however, hardly affect the weight curves during the first 15 months. The present series shows that tumour-positive status, defined as microscopic ingrowth into the resection margins and tumour recurrence, are important factors determining weight gain after pancreatoduodenectomy. These factors seem to be of more importance for postoperative weight gain than the type of surgical procedure carried out. Patients with a positive tumour status showed a significant decline in weight. At 15 years of operation patients with positive tumour status had lost 23 and 17 per cent of their usual weight, for standard and pylorus-preserving resection respectively. In none of the groups was mean pre-illness weight reached. At 15 months after operation patients with a negative tumour status regained 94 per cent of pre-illness weight. In an early study Braasch *et al.*[18] reported similar results in 28 patients after PPPD who regained a mean body-weight of 93 per cent of pre-illness weight[18]. In another study patients after PPPD regained 95 per cent of the weight that was lost before operation[19]. In both studies positive tumour status was not taken into account and a large proportion of the patients had undergone resection for chronic pancreatitis[18,19]. In a study by Zerbi *et al.*[13], weight at 6 months after operation was significantly better following PPPD than standard resection: 92 and 86 per cent of pre-illness weight respectively. Patients with tumour recurrence during these 6 months were not taken into account in this analysis[13].

PPPD has been reported to be a good alternative to the standard Whipple resection. Although some authors advise against PPPD for periampullary cancer[11,20], in most studies similar postoperative morbidity and mortality and 5-year survival rates are reported compared with the standard Whipple resection[10,14,21,22]. PPPD is therefore accepted in most centres as a standard resection for ampullary and periampullary cancer. Moreover, in the present series none of the patients with microscopically non-radical resection showed ingrowth into the duodenal resection margin.

Morbidity and mortality rates were no different for the two procedures, but the present series does show a shorter operating time, less peroperative blood loss and subsequently a lower transfusion need for the pylorus-preserving resection. In another study in which the authors investigated delayed gastric emptying after standard Whipple resection and PPPD, similar results were found[23]. These results may also be a reflection of the fact that most of the standard Whipple resections were performed at an earlier point in time. A learning curve might have played a role in these results. Another contributing factor is the different reconstruction that was used for pancreatoduodenectomies performed after 1993, using one jejunal loop, a single-layer pancreatic anastomosis and without placement of a transanastomotic drain in the pancreatic duct. Others, however, have reported similar advantages for PPPD[14,24].

The present series shows a slightly lower number of patients needing pancreatic exocrine supplementation after PPPD than after standard Whipple resection. Postoperative radiotherapy could cause pancreatic exocrine insufficiency, but in the present study a similar number of patients was treated with postoperative radiotherapy and chemotherapy after both procedures. Others have also reported a lower number of patients with pancreatic exocrine insufficiency after PPPD compared with standard pancreatoduodenectomy[17].

In conclusion, postoperative weight gain was no different for patients who underwent standard Whipple resection or PPPD in the first 15 months after resection. Tumour-related factors such as ingrowth into the resection margins and recurrence are probably more important with respect to weight gain in these patients than is the type of resection. Most patients, however, do not return to their pre-illness weight after either procedure.

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Different gastric emptying of solid and liquid meals after pylorus-preserving pancreatoduodenectomy

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Background Transient gastric stasis immediately after pylorus-preserving pancreatoduodenectomy (PPPD) is a common complication, but the cause remains unknown. Changes in gastric emptying were investigated in patients undergoing PPPD for periampullary malignancy.

Methods In 14 patients undergoing PPPD, liquid- and solid-phase gastric emptying were evaluated before and after operation (mean 38 (range 27–53) days after operation). Two pharmacological gastric-emptying tests were used: the acetaminophen test for liquid-phase emptying and the sulphamethizole capsule food test for solid-phase gastric emptying.

Results All patients exhibited delayed solid emptying but fairly good liquid emptying.

Conclusion Gastric function in the early postoperative period after PPPD is characterized by delayed solid-phase but good liquid-phase emptying.

Pylorus-preserving pancreatoduodenectomy (PPPD) was first reported by Watson[1] and reintroduced by Traverso and Longmire[2] in 1978; it has become the standard surgical procedure for benign or malignant periampullary lesions. Although this procedure eliminates the postgastrectomy symptoms that are common after the classical Whipple procedure, transient gastric stasis immediately after operation has been a frequent complication[3–6]. The cause of this complication remains unknown.

Some authors have measured gastric emptying some months after PPPD[7–9]; they showed recovery in the late postoperative period. However, there have been few reports of solid and liquid gastric emptying in the early postoperative period. Early function after operation is usually expressed clinically as the duration of nasogastric decompression or the inability to tolerate solid food.

Gastric emptying was measured using pharmacological tests at a mean of 38 days after PPPD. The indirect gastric emptying tests utilized two pharmacological markers: powdered acetaminophen (paracetamol), and pelletized sulphamethizole. The markers were ingested simultaneously with 250 ml water and the serum drug concentrations were assayed. These tests (the sulphamethizole capsule food test[10] and the acetaminophen test[11,12]) are based on the fact that absorption of the marker agents depends on the rate of gastric emptying[13,14]. Acetaminophen is emptied from the stomach with the water and pelletized sulphamethizole is dealt with as a solid by the stomach.

Patients and methods

From March 1992 to May 1993, 19 patients with periampullary lesions underwent PPPD in the authors' department. The operation included resection of the head of the pancreas, the duodenum distal to the first portion, a short segment of the proximal jejunum, the gallbladder and the common bile duct. Regional lymph node dissection around the common hepatic, coeliac and superior mesenteric arteries, and the abdominal aorta was also performed. The pancreatic remnant, common hepatic duct and the first portion of the duodenum were anastomosed to the jejunal loop in an end-to-side fashion, in this order. Five of the patients were excluded: three refused gastric emptying testing, one underwent PPPD without lymph node dissection and one required antidepressants in the postoperative period. The latter patient was excluded because of the possible influence of the antidepressants on gastric emptying.

Informed consent was obtained from all patients and the study was approved by the human research review committee of Nagoya University Hospital.

Preparation of sulphamethizole capsules

The sulphamethizole capsules were prepared according to the method of Asada *et al.*[10]. Chicken egg albumin (1·69 g) (Katayama Chemical, Tokyo, Japan), sulphamethizole (0·56 g) (Urocydal; Eizai, Tokyo, Japan), powdered acacia (0·38 g) (gum Arabic powder; Katayama) and distilled water (4·87 g) were mixed. The mixture was steamed for 8 min in a steel case until solidified. After it had cooled, 15 hard gelatin capsules (no. 1) were filled with this solid matter.

Gastric emptying tests

A combined direct gastric emptying test was performed to evaluate preoperative and postoperative function. The test was scheduled within 5 days of operation and at a mean of 38 (range 27–53) days after surgery.

After an overnight fast each patient was given 15 sulphamethizole capsules and 0·75 g acetaminophen (Napa; Astra Japan, Osaka, Japan) with 250 ml of warm (body temperature) water. The patients sat at ease and were prohibited from drinking, eating or smoking during the test. Venous blood samples were taken every 30 min until 4 h after ingestion. The blood samples were centrifuged at 3000 r.p.m. for 10 min, and the serum was stored at −20°C until assayed.

Measurement of drug concentration in the blood samples

Serum sulphamethizole concentrations were measured with a high-performance liquid chromatography system (HPLC). Serum

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was mixed with a double volume of acetonitrile, shaken for 2 min and filtered (Millex-GV 0·2 μm; Millipore Products Division, Bedford, Massachusetts, USA). The filtrate (20 μl) was injected into the HPLC apparatus (Shimadzu LC-6A system; Shimadzu, Kyoto, Japan), which was equipped with an STR-ODS II column (Shimadzu). The mobile phase was a mixture of acetonitrile and 1 per cent acetic acid at 13:87 (v:v), which ran at a rate of 1 ml/min. The peaks of sulphamethizole appeared approximately 13 min after injection at room temperature. Sulphamethizole concentrations were calculated using the Chromatopack 6A system (Shimadzu) and a standard curve.

Serum acetaminophen levels were analysed by means of fluorescence polarization immunoassay (FPIA). Serum (50 μl) was placed in test tubes on the carousel of the fully automated FPIA apparatus (TDX; Dainabot, Tokyo, Japan). Reagents were supplied commercially as a kit (Dainabot).

Results were adjusted according to body-weight using the following formula: (adjusted drug concentration) = (analysis results) × (body-weight (kg))/60 (kg).

Statistical analysis

Results are expressed as mean(s.d.). Statistical analysis was performed with the paired Wilcoxon test. $P<0{\cdot}05$ was considered statistically significant.

Results

Clinical data

There were 14 patients (seven men and seven women) enrolled in the study with a mean age of 62·5 (range 41–73) years. All patients had periampullary malignancy diagnosed before operation (two papillary, five bile duct and seven pancreatic head cancers). Three patients with diffuse bile duct carcinoma also underwent combined PPPD and liver resection[15]. The mean length of the proximal duodenal remnant was 2·4 (range 1–4) cm.

There were four postoperative complications in four patients (anastomotic leakage, cholangitis, pancreatitis and inter-abdominal infection), but no hospital deaths. The mean duration of gastric decompression via tube gastrostomy was 11 (range 3–27) days. A liquid diet was commenced 16 (range 8–29) days after operation). Solid food was started 33 (range 20–50) days after surgery).

Solid- and liquid-phase gastric emptying

Solid-phase gastric emptying was delayed in the postoperative period (*Fig. 1*). The rise in the mean postoperative sulphamethizole concentration was slower, and the peak was lower and appeared later than in the preoperative period. The mean(s.d.) peak value was 3·58(1·40) μg/ml at 150 min before operation and 2·08(1·15) μg/ml at 180 min after operation. At each time point during the 4 h, the differences between preoperative and postoperative results were statistically significant ($P<0{\cdot}05$). In all patients the postoperative serum sulphamethizole concentration at 120 min was lower than the corresponding preoperative value (*Fig. 2*).

Differences in liquid-phase emptying were less pronounced (*Fig. 3*). Mean(s.d.) preoperative and postoperative peaks were 11·9(1·6) and 10·4(2·8) μg/ml at 60 min. The rise in the mean acetaminophen concentration was slower in the postoperative than in the preoperative period. However, differences were not significant ($P=0{\cdot}07$, $P=0{\cdot}07$ and $P=0{\cdot}96$ at 30, 60 and 90 min respectively), except at 120 min ($P<0{\cdot}01$). The individual changes at 60 min exhibited no apparent tendency toward delayed gastric emptying in the postoperative period (*Fig. 4*).

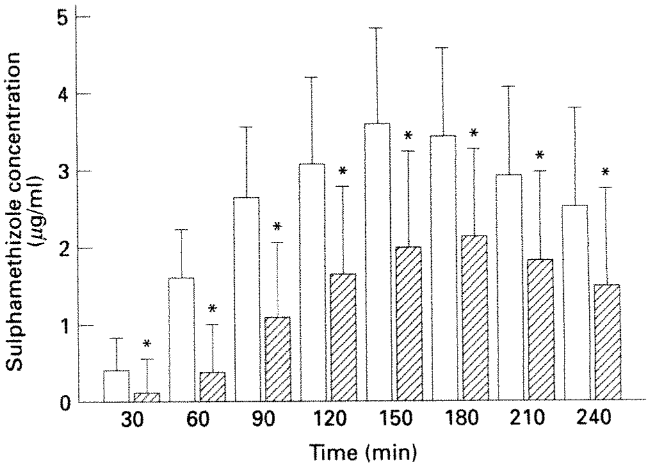

Fig. 1 Solid-phase gastric emptying before (□) and after (▨) pylorus-preserving pancreatoduodenectomy expressed as serum sulphamethizole concentration. Values are mean(s.d.). $^*P<0{\cdot}05$ *versus* preoperative value (paired Wilcoxon test)

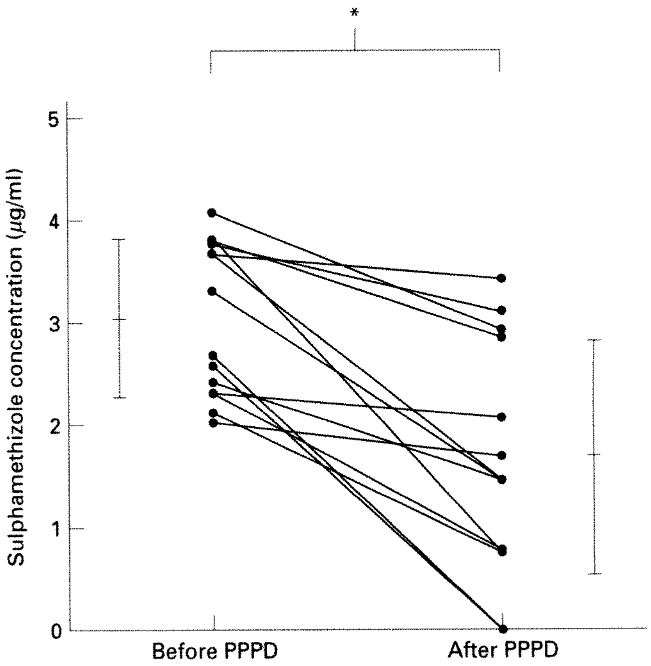

Fig. 2 Individual changes in solid-phase gastric emptying after pylorus-preserving pancreatoduodenectomy. Values are sulphamethizole concentrations 120 min after ingestion. Bars denote mean(s.d.) values. $^*P<0{\cdot}05$ (paired Wilcoxon test)

Discussion

PPPD has been reported to minimize postgastrectomy symptoms in patients undergoing resection of the head of the pancreas and the duodenum, by preserving gastric reservoir function[16]. The present authors have shown previously that oral caloric intake 6 weeks after operation is significantly better in patients undergoing PPPD than in those having classical pancreatoduodenectomy[17]. Post-

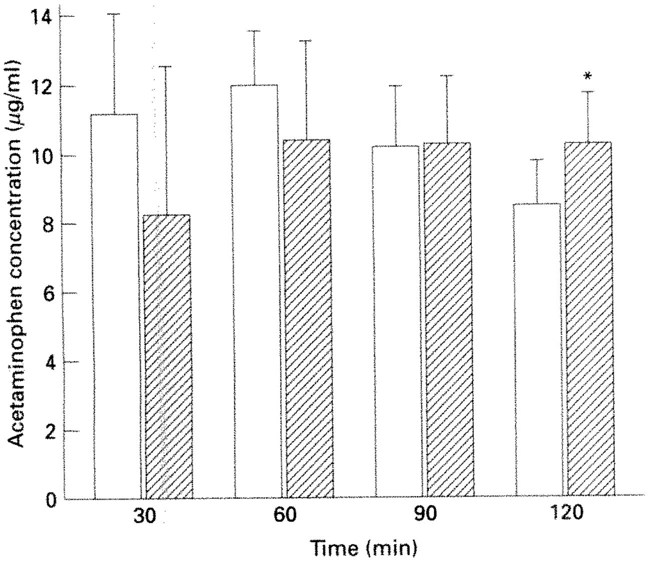

Fig. 3 Liquid-phase gastric emptying before (□) and after (▨) pylorus-preserving pancreatoduodenectomy expressed as serum acetaminophen concentration. Values are mean(s.d.). $*P < 0.01$ *versus* preoperative value (paired Wilcoxon test)

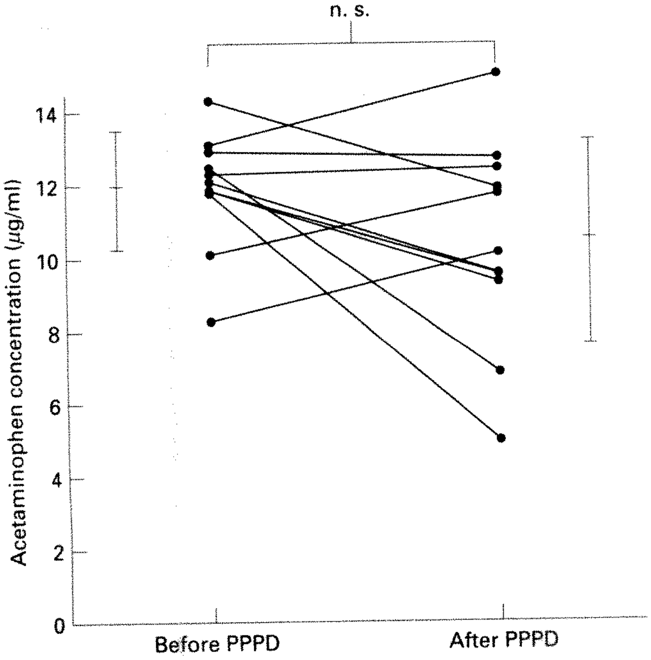

Fig. 4 Individual changes in liquid-phase gastric emptying after pylorus-preserving pancreatoduodenectomy. Values are acetaminophen concentrations 60 min after ingestion. Bars denote mean(s.d.) values. n.s., *P* not significant

prandial plasma gastrin and secretin levels are similar in patients having PPPD and controls[18].

However, functional recovery of the preserved stomach and the first portion of the duodenum requires several days or weeks. Yeo and colleagues[19] showed delayed solid and liquid gastric emptying on the tenth postoperative day and documented the effectiveness of erythromycin for this problem. On the other hand, Hunt and McLean[8] reported normal solid and liquid gastric emptying in six of nine patients 3 months after PPPD. Williamson *et al.*[9] studied liquid and solid gastric emptying in 24 patients who had undergone PPPD and reported that late delay in gastric emptying was uncommon. In the present study gastric emptying was measured in 14 patients who had PPPD around the sixth postoperative week, and delayed emptying of solids with well recovered liquid emptying was found.

The different intervals between the operation and measurement of gastric emptying in the various studies may explain the variable results. This suggests that there is a pattern of recovery of gastric emptying after PPPD. Immediately after operation both phases of gastric emptying are disturbed. Liquid-phase gastric emptying recovers within several weeks. Finally, solid-phase gastric emptying recovers.

Physiologically, solids are pushed aborally with phasic motility of the distal stomach, and liquids flow through the pylorus with tonic contraction of the proximal stomach. This functional difference in gastric emptying may relate to the stepwise recovery of function after PPPD.

The precise cause of the dysfunction of gastric emptying after PPPD remains unknown. Many factors, including pancreatic fistula and perihepatic abscess[8,20], injury to the duodenal neurovascular supply[16,21], gastric atony secondary to decreased plasma motilin concentration[19,22] and transient torsion or angulation of the reconstructed alimentary tract[23], have all been proposed.

There have been no previous reports of the different disturbances in solid- and liquid-phase gastric emptying in the early period after PPPD. However, this kind of gastric emptying dysfunction is well known in patients with diabetic or postvagotomy gastroparesis, both of which result from impaired neural control[24–27]. In PPPD, the neural supply to the stomach is usually preserved, while the vagal branches to the pylorus and the first portion of the duodenum are sometimes injured. Dysfunction of the pylorus and duodenum may be a factor in delayed gastric emptying after PPPD.

In this study gastric emptying was evaluated by means of indirect pharmacological tests. Heading and colleagues[11] reported a significant correlation between the isotopic gastric emptying half-time and plasma acetaminophen concentration. A quick rise in the blood drug concentration suggests rapid gastric emptying. On the other hand, a slow ascent implies delayed gastric emptying[28,29]. This test has been used in patients who have undergone PPPD[23]. Sulphamethizole is a sulpha drug that is absorbed rapidly and almost completely when administered orally[30]. Asada *et al.*[10] pelletized sulphamethizole with egg albumin and used it as a marker of solid-phase gastric emptying. They reported that sulphamethizole absorption depended largely on the gastric emptying rate of the pellets[10]. Compared with dual-phase radioisotopic gastric emptying tests, which require a dual-head γ camera, this simple test is convenient and inexpensive.

In conclusion, the results of simple gastric emptying tests showed that liquid-phase gastric emptying had recovered and that solid-phase emptying was still disturbed 38 days after PPPD. This suggests a stepwise recovery of gastric emptying. Immediately after operation both liquid and solid phases of gastric emptying are disturbed. Liquid-phase emptying recovers within 2–5 weeks. Finally, solid-phase gastric emptying recovers approximately 3 months after operation. This type of gastric emptying disorder resembles that seen after vagotomy and in diabetic gastroparesis, both of which result from impaired neural control of the gastrointestinal tract.

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Effect of growth hormone treatment on the healing of left colonic anastomoses in protein-malnourished rats

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Background Malnutrition is known to affect wound healing but it is not known with certainty whether or not postoperative hyperalimentation can reverse this defect. The present study was designed to examine the effects of recombinant human growth hormone (hGH) on left colonic anastomoses in malnourished rats.

Methods Experimental animals were allocated randomly into four groups. In groups 1 and 2 animals were fed with normal diet for 10 days before surgery. In groups 3 and 4 animals were fed with a low-protein diet. Left colonic anastomoses were performed in all animals. Following surgery, rats in groups 1 and 3 received hGH whereas rats in groups 2 and 4 were injected with saline as control. Bursting pressure and hydroxyproline levels on day 4 after operation were used to determine anastomotic healing.

Results Bursting pressure was lower in the malnourished rats than those fed with normal diet ($P < 0·05$). Bursting pressure was higher in normally fed rats which were given hGH. No significant differences could be noted between malnourished control rats and those receiving hGH.

Conclusion These results suggest that hGH strengthened the left colonic anastomoses in rats fed a normal diet, but could not reverse the negative effects of malnutrition on colonic anastomoses.

Anastomotic leakage after colonic resection is a serious complication with high morbidity and mortality[1,2]. Surgical technique, ischaemia, nutritional status of the patient, irradiation and presence of diabetes mellitus impair anastomotic healing[3,11].

Malnutrition is known to have a deleterious effect on wound healing, but it is not clear whether postoperative hyperalimentation can reverse this defect. The effects of duration of protein restriction and postoperative amino acid replacement on anastomotic healing are also unclear[4,6,8,11].

Previous studies in rats have shown that human growth hormone (hGH) (Genotropin; Pharmacia, Istanbul, Turkey) accelerates wound healing and strengthens colonic anastomoses[12–17]. The effect of hGH on colonic anastomosis in malnourished rats has not been studied previously. Thus, it may be hypothesized that hGH could overcome the negative effects of malnutrition on anastomotic healing.

The present study investigated the effect of hGH on left colonic anastomosis in malnourished rats that were fed with a low-protein diet for a short time.

Materials and methods

Forty male Sprague–Dawley rats weighing 220–260 g were allocated randomly into four identical groups. In groups 1 and 2 animals were fed with normal diet for 10 days before surgery (3·6 g/protein, 40 kcal per day). In groups 3 and 4 animals were fed with a low-protein diet (1·2 g protein, 40 kcal per day) for 10 days before surgery. All animals had free access to the standard laboratory diet and water after surgery. Before operation all animals were kept in separate cages and changes in weight were noted.

Surgical procedure

The animals were anaesthetized by an intramuscular injection of ketamine hydrochloride (50 mg per kg of body-weight). A midline laparotomy incision was made and a 1-cm segment of left colon was resected 3 cm proximal to the peritoneal reflection. The faecal contents were milked out and a standardized end-to-end anastomosis was performed with inverting 6/8 polypropylene sutures. The abdominal wall was closed with a single layer of 3/0 silk. After 24 h the animals were allowed to resume their respective diets.

In groups 1 and 3 rats were given hGH subcutaneously at the back of the neck in a dose of 2 mg per kg per day for 4 days beginning on the operation day. In groups 2 and 4 equivalent volumes of saline were injected.

Four days after operation the abdominal incision was reopened. The anastomotic segment was resected preserving the adhesions which were 2 cm proximal and 2 cm distal to the anastomotic line. The bursting pressure of the anastomotic segment was measured with a mercury manometer and a constant flow pump (Perfusor Secura FT; B. Braun, Germany). Following this procedure the bowel was opened longitudinally. The whole tissue in the area between 4 cm proximal and 4 cm distal to the anastomotic line was stored at −40°C for hydroxyproline determination. Hydroxyproline determination was performed by spectrophotometry at 560 nm by the technique described by Dekker *et al.*[18].

Data are expressed as mean(s.d.). Analysis of variance was used for statistical analysis and $P < 0·05$ was considered significant.

Results

One rat in group 3 and one from group 4 died on day 3 after surgery from sepsis resulting from anastomotic dehiscence.

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Body-weight was constant in rats fed on a normal diet ($P > 0{\cdot}05$), but there was a fall of 15 per cent in the groups fed on a low-protein diet until surgery ($P < 0{\cdot}05$). Following surgery rats fed on a normal diet which received hGH had a 2 per cent increase in body-weight, but the groups receiving saline had a 2 per cent decrease in body-weight ($P < 0{\cdot}05$). Weight loss continued in malnourished rats after surgery (5 per cent in saline group, 3 per cent in hGH group) ($P < 0{\cdot}05$) (*Fig. 1*).

Bursting pressure of the anastomotic segments was lower in malnourished rats than in normally fed rats ($P < 0{\cdot}05$). In the normal diet groups, bursting pressure values in the hGH injected rats were 10 per cent higher than in the saline injected group ($P < 0{\cdot}05$). No significant difference existed between the hGH and saline groups of malnourished rats (*Table 1*).

In group 1, hydroxyproline levels were 9 per cent higher than in group 2 ($P > 0{\cdot}05$). There was no significant difference between the normal and malnourished rats which were injected with saline. No significant difference could be noted between hGH and saline groups among malnourished rats.

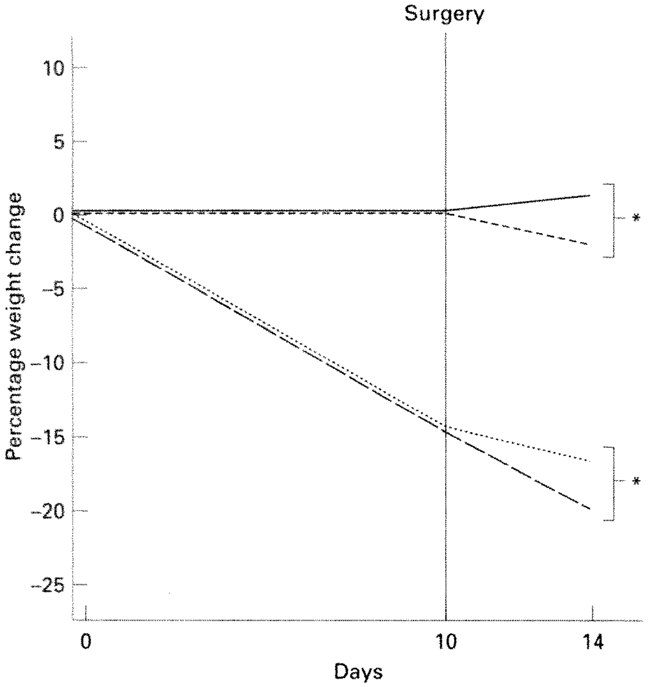

Fig. 1 Percentage weight change 10 days before and 4 days after surgery. Rats on normal diet receiving b-hGH (group 1, ———); rats on normal diet receiving saline (group 2, - - - -); protein-malnourished rats receiving b-hGH (group 3, ·····); protein-malnourished rats receiving saline (group 4, — —). $^*P < 0{\cdot}05$

Discussion

Delayed wound healing is seen in malnourished patients undergoing surgery[19]. Wound healing is inhibited by accelerated catabolism and protein consumption in the early postoperative period[6]. Previous experimental studies have reported the detrimental effects of malnutrition on the healing of colonic anastomoses[4,6,8,11]. Ward *et al.*[6] have reported that anastomotic healing was impaired in rats which lost 12·5 per cent of their body-weight resulting from protein restriction. Likewise, Daly *et al.*[4] reported that colonic bursting pressures decreased by 17·5 per cent during a week-long protein restriction in rats. In the present study, the effect of postoperative hGH on anastomotic healing was examined by creating a similar model of protein malnutrition to that observed in surgical patients. As weight loss in surgical patients is usually about 12·5 per cent[20], a similar condition was created in the present study. As a result, anastomotic healing was impaired in rats with a weight loss of 15 per cent. The most likely reason for impairment is the effect of protein restriction on amino acid bioavailability.

Growth hormone accelerates cell proliferation and enhances amino acid efflux into the cells for protein synthesis or gluconeogenesis[21–23]; it also provides protein anabolism by enhancing nitrogen uptake and preventing the loss of protein[22–26], and is known to be an effective anabolic hormone preventing postoperative weight loss[15,16]. In this study hGH intake led to significantly increased body-weight when control animals were compared with the normal diet groups, but in malnourished rats weight loss occurred both in the hGH and saline-treated groups.

In the present study bursting pressure increased with hGH in normally fed rats; these results are similar to those of Christensen *et al.*[12–16]. An anastomoses is at its weakest on days 2 and 3 when the repair of new collagen cannot be completely organized instead of the collapsed old collagen[27]. In this study anastomotic healing was evaluated on day 4 after surgery. The fact that bursting pressure significantly increased in rats on a normal diet compared with controls suggests that hGH is effective in the early phase of healing. The mechanism of action of hGH on the healing of anastomosis in the early phase has not been explained completely as the anastomosis is weakest in the early postoperative period. The probable causes of the rapid response to hGH stimulation are fibroblast stimulation and hGH receptors in rat colon[16,28]. The effects of hGH are related to insulin like growth factor (IgF) I produced in liver, IgF-I receptors in the

Table 1 Bursting pressure and hydroxyproline levels of left colonic anastomoses on day 4 after surgery in rats on a normal diet receiving b-hGH (group 1); rats on a normal diet receiving saline (group 2); protein-malnourished rats receiving b-hGH (group 3); and protein-malnourished rats receiving saline (group 4)

	Normal rats			Malnourished rats		
Treatment	hGH	Saline	*P*	hGH	Saline	*P*
Bursting pressure (mmHg)	50·6(4·2)	45·0(5·3)	< 0·05	42·3(3·6)	41·2(3·5)	> 0·05
Hydroxyproline (μg/100 mg)	0·067(0·005)	0·061(0·007)	< 0·05	0·059(0·006)	0·058(0·003)	> 0·05

Values are mean(s.d.)

gastrointestinal tractus and hGH receptors recently discovered in the rat colon[13,14,29,30]. Christensen *et al.*[15,16] reported in their consecutive studies that hGH not only influences cells that have been stimulated before the operation but also during the period of healing itself.

Contrary to expectations, hGH could not influence anastomotic healing in rats which lost 15 per cent of their body-weight. The possible reasons for this may be: (1) the short duration of treatment; (2) the standard single-dose therapy; and (3) protein deprivation. The stimulatory effects of hGH on wound and anastomotic healing and its relation to dose and time have been reported by various authors[3,12–15,17]. At present the effects of hGH on anastomotic healing are unclear and this fact necessitates further studies on the efficacy of hGH in malnutrition.

The present study established that hGH strengthened left colonic anastomoses in well nourished rats but did not reverse the negative effects of malnutrition on anastomotic healing. Further detailed studies with different durations and doses are necessary to determine whether hGH can improve anastomotic healing.

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Long-term results of femorotibial bypass with vein or polytetrafluoroethylene

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Background This was a retrospective review of the long-term results of femorotibial bypass using autologous vein and polytetrafluoroethylene (PTFE) over 24 years.

Methods Some 518 patients who underwent 635 femorotibial bypass grafts were studied. Outcome measures analysed included primary and secondary graft patency, limb salvage rates and death.

Results Overall primary and secondary graft patencies were 62 and 67 per cent respectively at 12 months, and 44 and 48 per cent at 24 months. For vein grafts, the primary and secondary patencies were 63 and 66 per cent at 12 months, and 54 and 56 per cent at 24 months. For PTFE grafts, the primary and secondary patencies were 48 and 54 per cent at 12 months, and 31 and 37 per cent at 24 months. Limb salvage and patient survival rates were 81 and 84 per cent at 12 months, and 73 and 74 per cent at 24 months. Primary and secondary graft patencies for vein were significantly better than for PTFE ($P = 0{\cdot}0001$). There was no difference in patency between reversed and *in situ* grafts.

Conclusion Femorotibial bypass can produce excellent long-term results. Vein remains the conduit of choice but in the absence of vein acceptable results can be achieved with PTFE.

Femorotibial bypass is an acceptable technique for revascularizing a critically ischaemic leg and avoiding a major amputation[1–5]. It can be a demanding operation with a long learning curve and good results may be achieved only by surgeons who perform the operation regularly. Autologous saphenous vein has the best patency and limb salvage rates. Many patients do not have suitable or available saphenous vein. The use of prosthetic grafts remains controversial despite enthusiasts who claim good results for polytetrafluoroethylene (PTFE) bypass to distal sites[6]. Many surgeons advocate the use of adjuvant techniques such as vein cuffs, patches and fistulas[7,8]. The Royal Adelaide Hospital has an extensive experience of femorotibial bypass with both vein and PTFE over nearly a quarter of a century. This paper presents the long-term results of this experience.

Patients and methods

All patients who had femorotibial bypass between August 1971 and December 1995 were entered on a computerized vascular database. This enabled evaluation of the outcome of surgery and follow-up. The Royal Adelaide Hospital is a teaching hospital in South Australia and has a wide catchment area extending into New South Wales and the Northern Territories with a population of over one million. Patients were admitted for non-invasive assessment, control of medical risk factors and angiography. The operation was usually performed under general anaesthesia and completion angiography was performed routinely. The technique of forming a Miller vein cuff has been reported previously[7]. Follow-up was by regular clinical examination and ankle–brachial pressure measurement. Limited duplex graft surveillance[9] was available during the later years but some patients lived too far away to be able to participate in any useful surveillance programme. In these cases outcome was determined by telephone interview with the patient and/or general practitioner.

Statistical analysis

Graft patency is reported according to the recommendations of the ad hoc committee of the Society of Vascular Surgery[10]. Primary graft patency is defined as uninterrupted patency with no procedures performed on the graft or its anastomoses. Secondary patency requires that flow is restored through most of the original graft including at least one of its original anastomoses. Actuarial patency curves were computed using the Kaplan–Meier method[11]. Multivariate analysis was performed on risk factors; however, the fact that some patients had multiple observations (i.e. several operations on one leg or operations on both legs) necessitated the use of the Wei–Liu–Weissfeld adaptation of the Cox proportional hazards regression procedure for comparison of risk factors and graft types and the multivariate analysis[12].

Results

Between August 1971 and December 1995, 518 patients had 635 femorotibial bypass procedures. The patient demographics are shown in *Table 1*. Some 361 procedures (57 per cent) were primary and 274 (43 per cent) were secondary in legs that had already undergone a distal graft. The graft details are shown in *Table 2* and inflow and outflow arteries are shown in *Table 3*.

Table 1 Patient demographics

No. of patients	518
Men	368 (71)
Women	150 (29)
Median (range) age (years)	72 (40–102)
Risk factors	
Ischaemic heart disease	248 (48)
Diabetes mellitus	187 (36)
Hypertension	200 (39)
Current or ex cigarette smoker	306 (59)

Values in parentheses are percentages

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Graft patency rates are shown in *Fig. 1*, and limb and patient survival rates in *Fig. 2*. The primary and secondary graft patencies were 62 and 67 per cent respectively at 12 months, and 44 and 48 per cent at 24 months. For vein grafts, the primary and secondary patencies were 63 and 66 per cent at 12 months, and 54 and 56 per cent at 24 months. For PTFE grafts, the primary and secondary patencies were 48 and 54 per cent at 12 months, and 31 and 37 per cent at 24 months (*Fig. 3*). Limb salvage and patient survival rates were 81 and 84 per cent at 12 months, and 73 and 74 per cent at 24 months. There was a significant difference between primary and secondary vein and PTFE graft patency (both $P = 0{\cdot}0001$). In PTFE grafts there was no significant difference between cuff *versus* patch or direct suture for primary and secondary patency ($P = 0{\cdot}75$). There were no significant differences in primary or secondary patency between reversed and *in situ* grafts ($P = 0{\cdot}54$) (*Fig. 4*).

Table 2 Graft details

	No. of grafts ($n = 635$)
Indication	
Intermittent claudication	21 (3)
Critical ischaemia	570 (90)
Acute ischaemia	39 (6)
False aneurysm/infected graft	5 (1)
Graft type	
Vein	251 (40)
PTFE	359 (57)
Composite	25 (4)
In situ vein	127 (51)
Reversed vein	124 (49)
Vein grafts ($n = 251$)	
Ipsilateral long saphenous	236 (94)
Contralateral long saphenous	4 (2)
Short saphenous	1 (0)
Arm	10 (4)
PTFE grafts and distal anastomosis ($n = 359$)	
Direct suture to artery	29 (8)
Vein cuff	288 (80)
Vein patch	42 (12)

Values in parentheses are percentages. PTFE, polytetrafluoroethylene

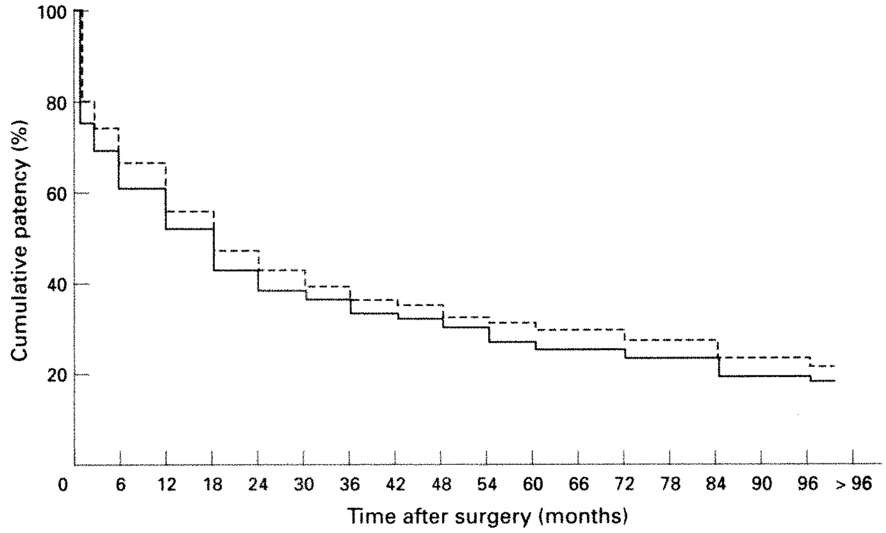
Discussion

Patients in this study were typical of those in other series; most had critical leg ischaemia although 21 patients (4 per cent) had severe claudication. An aggressive policy of femorotibial reconstruction was pursued in patients with severe ischaemia. This included re-do operations (43 per cent) in patients with blocked femoropopliteal or femorotibial grafts[13]. Patients usually had the operation on the first available daytime list which allowed 24–48 h for

Table 3 Inflow and outflow arteries

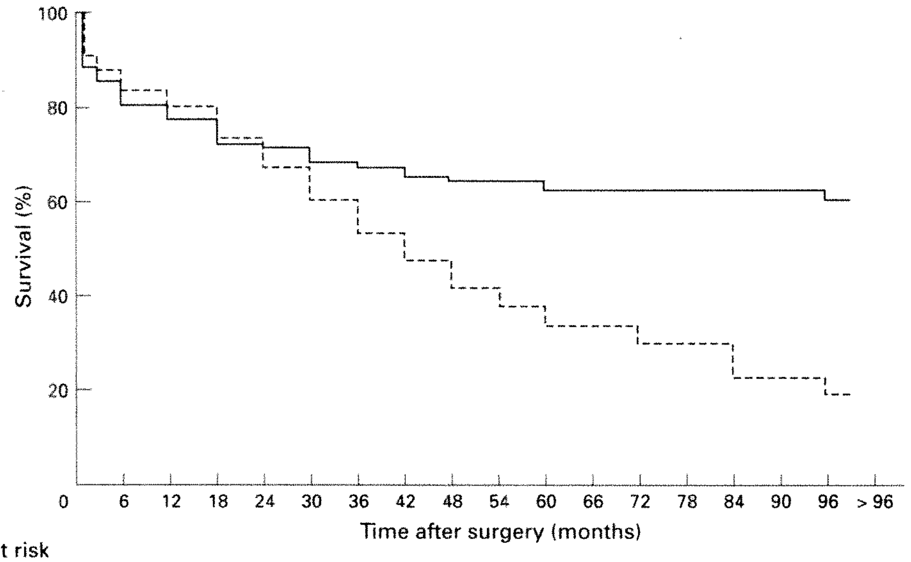
	No. of grafts ($n = 635$)
Inflow artery	
External iliac	11 (2)
Common femoral	419 (66)
Superficial femoral	59 (9)
Profunda femoris	3 (0)
Above-knee popliteal	22 (3)
Below-knee popliteal	29 (5)
Patent graft	92 (14)
Outflow artery	
Tibioperoneal trunk	69 (11)
Anterior tibial	152 (24)
Posterior tibial	221 (35)
Peroneal	193 (30)

Values in parentheses are percentages



No. at risk																
Primary patency	625	349	282	219	182	158	126	107	91	73	60		42		18		14	9
Secondary patency	623	371	300	233	199	166	132	111	95	81	69		49		25		20	15

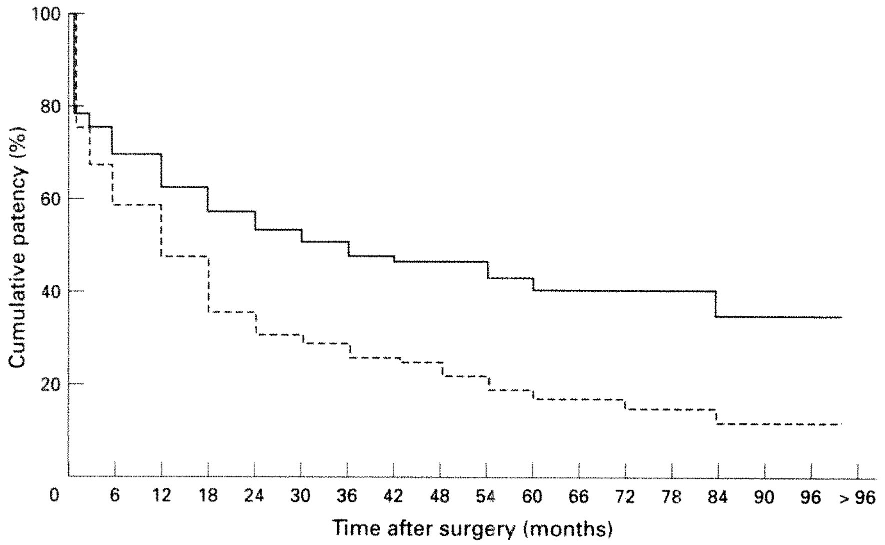
Fig. 1 Cumulative rates of primary (——) and secondary (- - -) graft patency. There were 635 grafts. Standard error is less than 10 per cent for all time points



No. at risk

	0	6	12	18	24	30	36	42	48	54	60	72	84	96	>96
Limb salvage	533	300	264	221	196	164	135	110	94	82	68	52	29	24	16
Patient survival	518	378	346	305	274	237	203	167	141	125	110	91	63	49	37

Fig. 2 Limb salvage (——) and patient survival (- - -). There were 556 limbs at risk and 518 patients. Standard error is less than 10 per cent for all time points



No. at risk

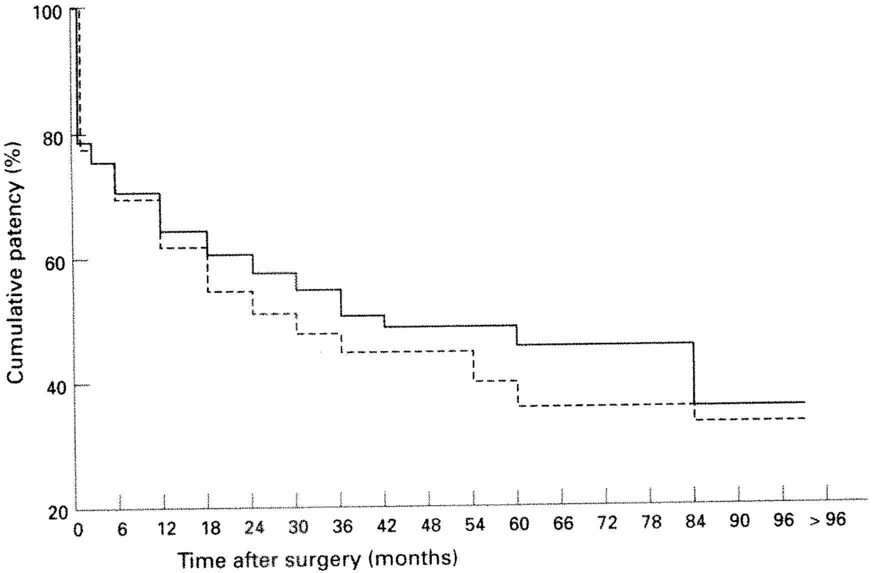
	0	6	12	18	24	30	36	42	48	54	60	72	84	96	>96
Vein grafts	247	153	128	109	91	77	62	50	46	38	32	23	11	10	6
PTFE grafts	353	190	149	107	89	78	61	54	42	32	26	17	5	3	3

Fig. 3 Primary graft patency for vein ($n = 251$, ——) and polytetrafluoroethylene (PTFE) ($n = 359$, - - -). Standard error is less than 10 per cent for all time points

an anaesthetic opinion and to treat any concurrent chronic medical disease. Patients who had no prospect of walking again because of dementia, severe arthritis, limb contractures or tissue necrosis extending into the weight bearing area of the foot were offered primary amputation.

Although ipsilateral long saphenous vein was used whenever available, only 40 per cent of patients in this series had a vein bypass. Arm vein was only used in 4 per cent of patients and only 2 per cent had contralateral long or short saphenous vein bypass. During this study, duplex assessment and vein mapping was not available. The introduction of this facility has increased the rate of vein utilization. In addition, the increasing prevalence of methicillin-resistant *staphylococcus aureus* infections has led to a more aggressive policy of using saphenous vein from the contralateral leg and also arm vein[14].

The results in this series are similar to others[5,15,16] in patients with severe ischaemia: limb salvage 81 and 73 per



No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96	> 96
In situ vein	123	76	62	53	44	38	28	25	22	19	15		10		1		1	1
Reversed vein	124	77	66	56	47	40	34	25	24	19	17		13		10		9	

Fig. 4 Primary graft patency for *in situ* (*n* = 127, ——) and reversed (*n* = 124, ---) vein grafts. Standard error is less than 10 per cent for all time points

cent at 12 and 24 months respectively and mortality rate 16 and 26 per cent at 12 and 24 months. As in other studies, patency in vein grafts was superior to that of PTFE, although there was no difference between reversed and *in situ* vein grafts. It is recognized that the long-term outcome in patients with severe leg ischaemia is poor; after 1 year, 25 per cent will have had an amputation and 25 per cent will have died[1]. The findings in this study are similar; at 5 years, the amputation rate was just below 40 per cent with a mortality rate of just under 70 per cent.

An aggressive policy of secondary femorotibial reconstruction has been followed using PTFE down to the ankle, if necessary, to achieve limb salvage. The majority of the PTFE grafts were fashioned in conjunction with a Miller vein cuff (80 per cent), with a vein patch or direct suture being the preferred technique in the remainder. The authors have previously reported superior patency rates for PTFE with a vein cuff to the below-knee popliteal artery[17]. In this non-randomized long-term review, there was no significant difference in patency for cuff *versus* patch or direct suture. The addition of a vein cuff can make a tibial anastomosis easier and preserves run-off should the graft thrombose. This allows easier surgical thrombectomy or thrombolysis.

The choice of vessel for the distal anastomosis was based on angiographic evidence of the most proximal disease-free vessel with good run-off into the distal circulation. Although pedal arch patency has been shown to be important for graft patency, its absence did not exclude patients from undergoing revascularization. The majority of grafts were to a calf vessel although 11 per cent had an anastomosis to the tibioperoneal trunk, if suitable. In most cases, there was only a single vessel run-off from the tibioperoneal trunk. Completion angiography was used routinely to exclude technical errors at the distal anastomosis.

Graft surveillance was difficult because of the geographical distances involved for many patients. A formal graft surveillance programme did not exist, although many local patients had 6-monthly duplex scans. A more rigorous and complete surveillance programme might have improved graft patency.

Femorotibial bypass can produce excellent results in patients with severe ischaemia. Autologous vein bypass produces the best results but acceptable results can be achieved with PTFE and a vein cuff, if vein is not available.

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Provision of training in carotid surgery does not compromise patient safety

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Background Vascular surgeons perceive that carotid endarterectomy carries a higher risk of stroke if performed by a surgical trainee. Accordingly, some trainees consider that they receive a less than adequate training in carotid surgery before taking up a consultant position. The aim of this study was to establish whether the stroke rate was adversely affected if carotid endarterectomy was performed by a surgical trainee under consultant supervision.

Methods This was a prospective study of 151 consecutive patients undergoing carotid endarterectomy between 1 January and 31 December 1996 using a standardized technique including intraoperative and postoperative transcranial Doppler monitoring and completion angioscopy.

Results The overall mortality and/or disabling stroke rate was 0·7 per cent (one of 151 patients), whereas the mortality and/or any stroke rate was 1·3 per cent (two of 151). Surgical trainees performed 82 of 151 carotid endarterectomies, with a mortality rate of 1 per cent and a mortality and/or any stroke rate of 2 per cent. There was no significant difference in the incidence of retained thrombus or intimal flaps between trainees and consultants as detected by angioscopy.

Conclusion Vascular surgical trainees can receive a comprehensive training in carotid artery surgery without incurring an unacceptable increase in operative risk.

Until the early 1990s, carotid endarterectomy was essentially a consultant-only procedure so as to minimize the operative stroke risk in the relatively small number of patients treated in the UK. However, following publication of the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[1,2], there has been a rapid increase in the annual number of carotid endarterectomies performed in the UK which, in Leicester, equated to a near sevenfold rise between 1990 and 1996.

In order that this large increase in workload is matched by an ongoing commitment towards minimizing the initial operative risk (and therein the overall clinical effectiveness of the operation) it is essential that a newly appointed consultant vascular surgeon has received comprehensive training in carotid surgery. There is still a genuine concern among some vascular surgeons that, by taking their trainee through the operation, an inevitable and unacceptable increase in operative morbidity will be incurred.

A prospective audit of the 30-day morbidity and mortality rates following carotid reconstruction for occlusive disease was analysed in a consecutive series of 151 patients. The aim was to see whether carotid endarterectomy performed by vascular surgical trainees was associated with an unacceptably higher operative risk.

Patients and methods

This prospective study included 151 consecutive patients undergoing carotid endarterectomy between 1 January and 31 December 1996.

Operative technique

Aspirin therapy was not stopped before surgery. All carotid reconstructions were performed under normocarbic, normotensive anaesthesia and systemic heparinization (5000 units) in a standard manner. A shunt (Pruitt–Inahara) was employed routinely, the proximal and distal intimal steps were tacked down with 7/0 polypropylene and all arteriotomies were closed with a collagen-impregnated Dacron patch (Vascutek, Glasgow, UK). If carotid bypass was required, this was performed using a segment of reversed saphenous vein harvested from the groin.

The operation was performed by a consultant vascular surgeon or by a specialist vascular trainee or overseas clinical vascular fellow. All trainees had completed at least 3 years of higher surgical training and were within 2 years of completing specialist vascular training. Operations were specifically undertaken by a consultant if they were an emergency referral (e.g. for crescendo transient ischaemic attacks (TIAs)) or if the patient was referred by a consultant surgeon from another health district. Otherwise there was no systematic policy for allocating trainee or consultant procedures.

Trainees in this institution commence carotid surgery by first performing individual phases of the operation such as carotid dissection, shunt insertion, endarterectomy and patch closure. Thereafter the trainee is permitted to perform an increasing amount of the procedure until the consultant is happy to delegate the full operation. Accordingly there is an element of case selection in that a less experienced trainee would not be allowed to perform the operation if preoperative studies suggested distal disease extension, but such a patient would be suitable for teaching a more experienced trainee. For the purposes of this study, therefore, the operation was attributed to a trainee only if he or she performed the entire procedure. If the consultant performed the operation or if the trainee did only part of it (e.g. the dissection phase), the operation and any complications were attributed to the supervising consultant.

Perioperative monitoring

Blood flow velocity in the middle cerebral artery blood (MCAV) was monitored continuously in patients with an accessible

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temporal window using transcranial Doppler (TCD) ultrasonography and a 2-MHz fixed-head probe system (Scimed, Bristol, UK). The surgeon was thereafter permitted to take any appropriate action to ensure optimal clinical outcome, for example embolization during dissection warned of an unstable plaque and permitted early internal carotid artery (ICA) clamping[3], while shunt malfunction (kinking, embolization, low flow) was immediately identified and corrected. The policy was to maintain a mean MCAV of 15 cm/s or more throughout the procedure, which on occasion required a therapeutic increase of arterial blood pressure by the anaesthetist[4].

Following endarterectomy and before complete closure of the patch, the shunt was removed and the carotid vessels were flushed and irrigated with heparinized saline and then reclamped. The lumen was inspected with a flexible fibreoptic hysteroscope to identify any residual technical error[5]. Policy was to remove any fragments of luminal thrombus and repair any intimal flap greater than 3 mm. Where necessary, an estimate of sizing of any luminal abnormality was done by comparison with the 2-mm diameter forceps that can be passed down the instrument channel of the hysteroscope.

Postoperative care

Patients recovered from anaesthesia in the operating theatre and were transferred to the high dependency unit where the TCD probe was reapplied to monitor ipsilateral MCAV for 10 min every 30 min for the next 6 h. In previous studies the authors have shown that embolic signals detected in the early postoperative phase are exclusively particulate[6], that sustained postoperative embolization is highly predictive of stroke as a result of carotid thrombosis[7,8] and that selective intervention with Dextran 40 therapy can reduce the risks of progression to carotid thrombosis[9]. Accordingly, any patient who had 25 or more emboli detected during any 10-min interval of monitoring was commenced on an incremental intravenous infusion of Dextran 40, starting at 20 ml/h. If the rate of embolization did not diminish, the infusion was gradually increased by 5 ml/h every 10 min to a maximum of 40 ml/h. Once the Dextran infusion rate was stabilized, it was continued at that dose for a further 12 h.

All patients were discharged home on aspirin (150 mg daily), usually on the fifth postoperative day, and all were reviewed 4–6 weeks later in the vascular clinic.

Results

Table 1 summarizes the patient demographics for the two study groups. There was no significant difference in either age or mode of presentation except that a consultant operated on all patients who presented with crescendo TIAs. Similarly, there was no significant difference in the patterns of concurrent disease.

Table 1 Patient demographics

	Operated on by vascular trainee ($n = 82$)	Operated on by consultant ($n = 69$)
Median age (years)*	68 (66–70)	67 (65–70)
Presentation†		
Stroke	32 (39)	25 (36)
TIA or amaurosis fugax	38 (46)	37 (54)
Asymptomatic	12 (15)	7 (10)
Urgent procedure	0 (0)	5 (7)
Concurrent disease†		
Hypertension	47 (57)	44 (64)
Angina pectoris	23 (28)	16 (23)
Previous MI	20 (24)	15 (22)
Diabetes mellitus	14 (17)	10 (14)

Values in parentheses are *95 per cent confidence interval and †percentages. TIA, transient ischaemic attack; MI, myocardial infarction

Table 2 Extent of carotid disease

	Operated on by vascular trainee	Operated on by consultant
Symptomatic patients		
Unilateral stenosis > 70%	45 (64)	40 (65)
Bilateral stenoses > 70%	12 (17)	13 (21)
Stenosis > 70%, contralateral occlusion	13 (19)	9 (15)
Total	70 (100)	62 (100)
Asymptomatic patients		
Unilateral stenosis > 70%	2	1
Bilateral stenoses > 70%	6	2
Stenosis > 70%, contralateral occlusion	4	4
Total	12	7

Symptomatic patients comprised 85 per cent of the operative workload of the trainees and 90 per cent of procedures performed by a consultant (*Table 2*). Overall, one-third of the symptomatic patients in the trainee- and consultant-operated groups had preoperative evidence of severe bilateral carotid artery disease. Almost one-fifth of the trainee operations were on symptomatic patients with a contralateral carotid occlusion (*Table 2*).

Some 144 patients (95·4 per cent) underwent a standard carotid endarterectomy, while seven needed carotid bypass (trainee, one; consultant, six). Carotid bypass was performed because of excessive kinking or looping of the distal ICA in five patients, and in two the residual arterial wall was very thin after endarterectomy and considered potentially unsafe. A further three patients (trainee, one; consultant, two) underwent formal shortening of the carotid bifurcation.

A consultant did not have to assume the role of principal surgeon in any operation that had been assigned from the outset to an experienced trainee.

Perioperative quality control

An accessible temporal window was present in 94 per cent of patients. TCD ultrasonography identified four patients with shunt malfunction. Three suffered inadvertent kinking of the shunt which was immediately recognized and corrected (trainee, two; consultant, one). In a further patient (consultant operation), ultrasonography indicated that the external carotid artery was the principal source of collateral blood supply to the brain. Accordingly the shunt was inserted into the external carotid while endarterectomy was performed.

All patients underwent completion angioscopy except for six of the seven undergoing carotid bypass. Angioscopic assessment was entirely normal in 95 per cent trainee procedures and in 94 per cent of consultant operations. A residual luminal thrombus was retrieved following one trainee endarterectomy and two consultant operations. Similarly, an intimal flap (greater than 3 mm) was detected and repaired in three and two operations respectively.

A total of 141 patients (93·4 per cent) underwent serial postoperative TCD monitoring. Of the ten not monitored after operation by ultrasonography (usually because of an inaccessible cranial window), none of the patients operated on by trainees but two in the consultant group

Table 3 Postoperative morbidity

	Operated on by vascular trainee ($n=82$)	Operated on by consultant ($n=69$)
Death or major stroke	1 (1)	0 (0)
Non-fatal minor stroke	1 (1)	0 (0)
Treatment for hypertension > 24 h	5 (6)	4 (6)
Heart failure	2 (2)	0 (0)
Treatment of arrhythmia	2 (2)	0 (0)
Unstable angina or myocardial infarction	1 (1)	2 (3)
Drainage of neck haematoma	2 (2)	4 (6)
Wound infection	2 (2)	1 (1)
Transfusion for anaemia	1 (1)	1 (1)
Pneumonia	1 (1)	0 (0)

were started on a Dextran infusion on the instructions of the operating consultant. Overall, three of 77 (4 per cent) of trainee operations monitored by ultrasonography developed sustained postoperative embolization which ceased following Dextran 40 therapy, compared with three (5 per cent) of 64 in the consultant group.

Perioperative morbidity and mortality

There was no significant difference in the 30-day morbidity and mortality rates between the two groups (*Table 3*). Eighteen patients (22 per cent) operated on by a trainee suffered some degree of morbidity compared with 12 (17 per cent) of the consultant operations.

Only one patient (trainee operation) suffered a fatal stroke following a computed tomography-verified intracranial haemorrhage on day 3. One other patient (trainee operation) suffered a non-fatal minor stroke with complete recovery.

Thus the overall mortality and/or rate of disabling stroke in 1996 was 0·7 per cent, whereas the mortality and/or any stroke rate was 1·3 per cent. Trainees performed 82 of 151 carotid endarterectomies with a mortality and/or disabling stroke rate of 1 per cent and a mortality and/or any stroke rate of 2 per cent. Consultants performed 69 carotid endarterectomies with no strokes or deaths occurring within 30 days of operation.

Discussion

The clinical effectiveness of carotid endarterectomy is inextricably linked to the initial operative risk. The lower the initial stroke risk, the greater the long-term benefit. The international trials reported a 5–7 per cent overall operative risk but despite this, carotid endarterectomy still conferred a 45 per cent relative risk reduction in the long-term stroke rate, when compared with best medical therapy alone. If the operative risk could be reduced to zero, the overall relative risk reduction would increase to 75 per cent[1,2]. Thus, centres with a higher operative stroke risk incur greater rehabilitation costs, prevent fewer strokes and may even become ineffective in terms of cost and/or clinical benefit. Moreover, surgeons must concede that the beneficial effects of carotid endarterectomy were proven in trials that allowed only surgeons with the lowest morbidity to participate. As a consequence, the ECST and NASCET results may not be applicable to all surgeons, all patients and all centres. For example, 47 (29 per cent) of 164 surgeons who applied to enter patients into the Asymptomatic Carotid Atherosclerosis Study were not approved following scrutiny of their centre's annual workload and track record[10]. This might explain why Medicare beneficiaries undergoing carotid endarterectomy at the same time as the NASCET study was being performed had an operative mortality rate of 3 per cent compared with only 0·6 per cent in NASCET[11].

The prevention of operation-related stroke therefore remains the goal of all vascular surgeons. The overall stroke risk is probably unrelated to anaesthetic practice[12] and the majority are due to inadvertent technical error[13]. Controversies about the role of temporary shunting, patch angioplasty, tacking sutures, quality control and perioperative monitoring persist, although relatively few studies have tried to standardize these and evaluate the impact of operative experience on outcome. There is evidence that surgeons who perform relatively few endarterectomies have a significantly higher stroke and/or death rate than more experienced colleagues[14]. Patients operated on by newly appointed consultant surgeons may be at a particular disadvantage.

This study has shown that vascular trainees can perform carotid endarterectomy with an acceptably low death and/or disabling stroke rate, in accordance with other similar studies[15,16]. An alternative conclusion might be that the study has simply confirmed that patients remain safer in the hands of a consultant surgeon. While this may well be the case, this study has shown that trainees' results can be equal to or better than those reported in the ECST or NASCET. Those who continue to assert that carotid endarterectomies must always be performed by a consultant surgeon must ask how they expect carotid surgeons of the future to be trained.

The low overall morbidity rate can be attributed to obsessional attention to detail, together with early recognition and correction of inadvertent technical error through the serial adoption of quality control and selected perioperative monitoring techniques[6–9]. In this respect, it was rewarding to observe that the incidence of technical error (as diagnosed by angioscopy) was no different between trainee and consultant-led procedures[17].

Exposure to a comprehensive carotid training programme appears to be variable. Recent evidence suggests that up to 90 per cent of vascular trainees in the UK have performed fewer than 20 carotid endarterectomies under consultant supervision, and 50 per cent performed fewer than ten. One-seventh of trainees had performed no carotid endarterectomies at all (J. H. N. Wolfe, data from the *1997 Annual Report of the Association of Surgeons of Great Britain and Ireland*). Even allowing for the effect of relative experience and stage of training, these data suggest that a significant number of surgeons approaching their first consultant post will probably have little carotid surgery experience. The system of training employed at this institution allows trainees of all grades to acquire progressively the operative skills they require. As a trainee becomes more proficient, it is essential that the supervising consultant adopts a less interventional role. The latter is one of the most difficult roles to balance but contributes towards a comprehensive training in carotid surgery.

The role of carotid endarterectomy has been proven unequivocally in selected patients, but surgeons must continue to strive to reduce operative risk. In this way the clinical and cost effectiveness of the procedure will increase. This not only entails attention to operative technique and avoiding inadvertent technical error, but also requires a renewed commitment to training the vascular surgeons of the future.

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Thermotolerance induces heat shock protein 72 expression and protects against ischaemia–reperfusion-induced lung injury

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Background Ischaemia–reperfusion injury is mediated by neutrophil–endothelial interaction. Induction of heat shock proteins attenuates neutrophil–endothelial interactions. The aim of this study was to determine whether thermal preconditioning could have a protective effect on neutrophil-mediated lung injury in an animal model of lower torso ischaemia–reperfusion.

Methods Sprague-Dawley rats were randomized into: control, ischaemia–reperfusion, and ischaemia–reperfusion preconditioned with hyperthermia groups. Ischaemia–reperfusion injury was induced by infrarenal aortic clamping for 30 min and reperfusion for 120 min. Thermotolerance was induced by raising the core body temperature to 40·5–41·5°C for 15 min, 18 h before ischaemia–reperfusion. Wet:dry lung (W:D) weight ratio, bronchoalveolar lavage protein (BAL_{prot}) concentration, tissue myeloperoxidase (MPO) activity and bronchoalveolar lavage polymorphonuclear neutrophil (BAL PMN) count were measured. Heat shock protein 72 (hsp72) expression in lung, intestine and mesentery was measured using Western immunoblotting.

Results Ischaemia–reperfusion resulted in a significant increase in tissue oedema (W:D weight ratio) and BAL_{prot} concentration. In addition there was a marked increase in tissue neutrophil infiltration (MPO activity, BAL PMN concentration). Preconditioning with hyperthemia resulted in increased expression of hsp72 and significantly reduced tissue oedema and neutrophil infiltration.

Conclusion Thermal preconditioning protects against neutrophil-mediated ischaemia–reperfusion-induced lung injury, possibly by increasing the expression of heat shock proteins.

Reperfusion of a large mass of ischaemic tissue, such as the lower torso, may induce systemic inflammatory reactions[1]. Severe and sometimes fatal pulmonary complications secondary to this inflammatory process have been described[2,3]. A key event in the pathogenesis of ischaemia–reperfusion injury is thought to be the interaction between activated neutrophils and the vascular endothelium[4–7]. Ischaemia–reperfusion results in upregulation of surface adhesion molecules and activation of circulating neutrophils which in turn adhere to the vascular endothelium and release oxidants and proteases which cause microvascular injury[8,9].

The heat shock or stress response refers to the process whereby stressful stimuli (e.g. hyperthermia) induce a transient resistance of the cells to subsequent noxious stimuli[10]. This resistance to oxidative stress is associated with an increased synthesis of highly conserved proteins called the heat shock proteins. Animal studies have shown that the heat shock response is protective against ischaemia–reperfusion-induced injury in the heart[11–13], small intestine[14], skeletal muscle[15] and kidneys[16]. The aim of this study was to evaluate the efficacy of thermotolerance in preventing ischaemia–reperfusion-induced lung injury in an animal model of lower torso ischaemia and reperfusion.

Materials and methods

Animal preparation

All animal procedures were carried out under licence from the Department of Health. Twenty-one adult male Sprague-Dawley rats weighing 350–400 g were randomized into three groups: control, ischaemia–reperfusion and a thermotolerant ischaemia–reperfusion group. Thermotolerance was induced 18 h before experimentation by increasing the core body temperature of the animals to 40·5–41·5°C by partial immersion in a water bath (Grant Instruments, Cambridge, UK) for 15 min[17] under anaesthesia with inhalational halothane (May and Baker, Dagenham, UK).

At the time of experimentation, animals were anaesthetized with inhalational halothane. The right internal jugular vein was catheterized for administration of heparin. All animals were maintained supine and core body temperature was monitored for the duration of the experiment by rectal probe (Hewlett-Packard, Boeblingen, Germany).

Aortic occlusion and reperfusion

Anaesthetized rats, including controls, underwent a midline laparotomy. In the ischaemia–reperfusion and ischaemia–reperfusion with hyperthermia groups the infrarenal abdominal aorta was exposed and after heparinization with 400 units heparin per kg body-weight a clamp was placed above the aortic bifurcation for 30 min. In control animals the aorta was exposed but not clamped. After 30 min of lower torso ischaemia the aortic clamp was removed through the previous laparotomy incision. Some 2 h after removal of the clamp the animals were killed.

Bronchoalveolar lavage

After sternotomy the left bronchus was clamped. Bronchoalveolar lavage (BAL) of the right lung was performed with 2 ml

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saline containing 0·07 mol/l ethylenediamine tetra-acetic acid. This was repeated three times. The combined lavage of approximately 4 ml was centrifuged at 1500*g* for 20 min at 4°C and frozen at − 20°C. BAL fluid was subsequently used for measurement of protein concentration (BAL_{prot}) by the spectrophotometric dye method of Lowry *et al.*[18].

Neutrophil count in BAL fluid (BAL PMNs) was used as a measure of pulmonary neutrophil influx and microvascular leakage. This was carried out by Diff-Quick staining of a representative sample of BAL fluid and consecutive counting of neutrophils per high power field.

Wet:dry lung weight ratio

Lung wet:dry (W:D) weight ratios were used as a measure of pulmonary oedema. The W:D weight ratio of the right lower lobe was calculated after weighing the freshly harvested organ, heating at 90°C in a gravity convection oven and repeatedly weighing the residuum until its weight became constant.

Myeloperoxidase assay

Myeloperoxidase (MPO) is a haem-containing enzyme which is found in neutrophils, and so can be used as an indirect measure of tissue neutrophil infiltration[19]. The right ventricle was cannulated with a 25-G needle and the right pulmonary hilum was clamped, after which the pulmonary vasculature of the left lung was 'washed out' with 50 ml normal saline. After weighing, the left lung was homogenized in 0·5 per cent hexadecyl trimethyl ammonium bromide (Sigma Chemical, St Louis, Missouri, USA). The supernatant was assayed spectrophotometrically for MPO activity. One unit of MPO was defined as that degrading 1 μmol peroxide per min at 25°C and calculated per g of tissue[20].

Western immunoblotting for heat shock protein 72 expression

Tissue samples from the lung, intestine and mesentery were removed, homogenized in cold phosphate buffer saline (1 ml) and centrifuged at 4100*g* for 30 min at 4°C. The supernatants were collected and protein concentration was quantified using a Coomassie protein assay reagent (Rockford, Illinois, USA). The final protein concentration of samples was diluted to 50 μg per 10 μl. The proteins were denatured at 100°C for 10 min and aliquots containing equal amounts of protein were then suspended in sodium dodecyl sulphate (SDS)–glycerol loading buffer (pH 6·8, 62·5 mmol/l Tris, 2 per cent SDS, 10 per cent glycerol, 5 per cent mercaptoethanol, 0·01 per cent bromophenol blue), and proteins were separated by SDS–polyacrylamide gel electrophoresis (ExcelGel, Pharmacia, Sweden) with 75 μg total protein loaded per lane. Proteins were then transferred to a nitrocellulose membrane (Sigma) and labelled with a primary monoclonal antibody (mbA), mouse antihuman immunoglobulin (Ig) G_1, specific for heat shock protein 72 (hsp72) (StrssGen, Victoria, British Columbia, Canada). After adding secondary mbA, sheep antimouse IgG_1 conjugated with alkaline phosphatase (Serotic, Oxford, UK), the protein was visualized using bromochloroindolyl phosphate–nitro blue tetrazolium (Sigma)[21].

Statistical analysis

All data are expressed as median (range). Kruskal–Wallis analysis of variance on ranks was used. If there was a significant difference between the groups, Student–Newman–Keuls multiple comparison procedure was applied. Statistical significance was set at $P < 0{\cdot}05$.

Results

Pulmonary microvascular leakage

Ischaemia–reperfusion resulted in a significant increase in pulmonary microvascular leakage compared with that in controls, as determined by wet:dry lung weight measurements and BAL_{prot} concentration. W:D weight ratios increased significantly from a median (range) control value of 3·72 (3·58–3·96) to an ischaemia–reperfusion value of 3·92 (3·86–4·80) ($P < 0{\cdot}05$). There was significant increase in BAL_{prot} concentration from control levels of 199·4 (135·9–280·3) μg/ml to ischaemia–reperfusion levels of 730·0 (373·5–1457·4) μg/ml ($P < 0{\cdot}05$). Thermotolerance resulted in a significant reduction in W:D ratio ((3·57) (3·33–3·70)) and in BAL_{prot} concentration (321·9 (193·2–245·1) μg/ml) compared with values in the ischaemia–reperfusion group ($P < 0{\cdot}05$).

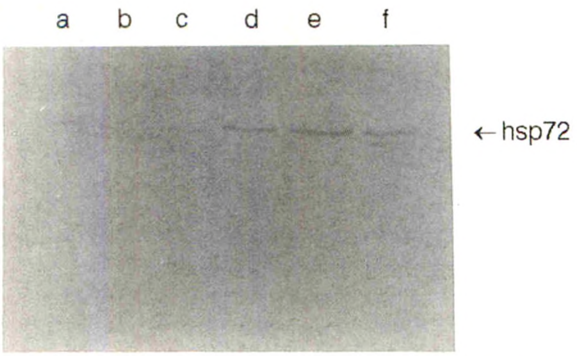

Fig. 1 Western immunoblotting for expression of heat shock protein 72 (hsp72) before ischaemia–reperfusion. Lanes d, e and f represent hsp72 in the lung, intestine and mesentery respectively in rats exposed to hyperthemia. Lanes a, b and c represent hsp72 in the lung, intestine and mesentery of rats not exposed to hyperthermia

Lung tissue neutrophil infiltration

Ischaemia–reperfusion resulted in significantly higher levels of MPO activity and BAL PMN count (3·91 (1·55–6·07) units/g and 3·5 (2·0–4·5) $\times 10^5$/ml respectively) compared with values in controls (1·25 (0·51–2·72) units/g and 0·5 (0·2–1·2) $\times 10^5$/ml respectively) ($P < 0{\cdot}05$).

In rats preconditioned with hyperthermia there was a significant reduction in MPO activity (1·89 (0·88–3·78) units/g) and in BAL PMN count (1·2 (0·2–1·5) $\times 10^5$/ml) compared with the ischaemia–reperfusion group ($P < 0{\cdot}05$).

Heat shock protein 72 expression

Fig. 1 demonstrates that hyperthermia induced expression of hsp72 in lung, mesentery and intestine. Some hsp72 activity was detected in lung tissue of non-heated animals. Previous studies in which densitometry was performed to measure the amount of hsp72 induced have also shown small amounts of hsp72 in tissues of control (non-heated) animals[11,14].

Discussion

The hypothesis was that thermal preconditioning *in vivo* might decrease lung injury secondary to lower torso ischaemia–reperfusion. This study confirmed that temporary clamping of the infrarenal aorta resulted in altered pulmonary endothelial barrier function, with oedema and increased BAL_{prot} concentration and neutrophil infiltration. Thermal preconditioning significantly decreased the lung injury. This was associated with increased expression of hsp72.

The authors and others have previously reported that aortic cross-clamping followed by reperfusion is associated with pulmonary injury and neutrophil activation[22–24]. Neutrophil activation has been implicated as one of the key mediators of distant organ damage and dysfunction caused by reperfusion injury[22,25]. The lung is particularly affected by this process. Recent studies have also confirmed the central role of the neutrophil in skeletal muscle, hepatic[26], myocardial[27] and pulmonary[22,26] injury following reperfusion. Adherence to endothelium is a prerequisite for microvascular injury. After adhering to pulmonary microvascular endothelium, neutrophils exert their toxic effects through the release of proteolytic enzymes and free radicals[22,26]. This is mediated by interaction between CD11b–CD18 adhesion glycoprotein complex expressed on neutrophils and its complementary ligand, intercellular adhesion molecule (ICAM) 1, on the endothelial cell.

Exposure of cells to a subcritical stress may protect cells and tissues from subsequent injury, possibly by inducing heat shock protein expression; this is referred to as thermotolerance. There is evidence to suggest that this phenomenon is mediated by heat shock proteins. Heat shock proteins represent a highly conserved family of constitutively expressed and stress-induced proteins. They act as molecular chaperones, playing a central role in the binding of denatured proteins[28,29]. *In vitro* studies have demonstrated that this effect is proportional to the amount of hsp72 present at the time of second injury[21,30]. *In vivo* studies have demonstrated that induction of hsp72, by heat stress, protects against ischaemia–reperfusion-induced renal, intestinal and other organ injury[14,17,31]. This study demonstrates that thermotolerance does induce expression of hsp72 in lung, mesentery and gut. Expression of the protein was associated with attenuation of ischaemia–reperfusion-induced acute lung injury.

The mechanism by which hsp72 or thermotolerance induces these changes is not clear. Thermotolerance decreases ischaemia–reperfusion-induced upregulation of ICAM-1 on the surface of renal endothelium[16]. Thermotolerance also decreases ischaemia–reperfusion-induced activation of the 5′-lipo-oxygenase pathway, decreasing synthesis of leukotriene B_4[14], which is known to induce leucocyte chemotaxis, adherence and degranulation[32]. It is possible that the protective effect of thermotolerance is through decreasing the synthesis of this molecule. There is also evidence that heat shock may enhance the cellular antioxidant defence system[33].

A hyperthermia-only group was not included in this study. This might have been useful in determining whether hyperthermia itself can lead to injury. However, previous studies have shown no significant difference in injury between animals treated with hyperthermia and controls[14,17]. The delay between induction of thermotolerance and the ischaemia–reperfusion injury was based on previous studies demonstrating that 18 h was optimal. Investigations are currently underway to establish pharmaceutical means of inducing this response over a shorter interval. As aortic aneurysm surgery is a planned procedure, preconditioning is an attractive method of reducing ischaemia–reperfusion injury. This could be particularly important in clinical practice if heat shock protein induction by pharmaceutical agents were shown to be effective in reducing the injury.

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Experimental study of the effect of adrenaline tolerance on intestinal ischaemia–reperfusion

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Background Adrenaline tolerance improves survival in animal models of shock. The purpose of this study was to determine the effects of adrenaline tolerance on intestinal ischaemia–reperfusion in a mouse model.

Methods Adrenaline tolerance was developed by injecting intravenous adrenaline, gradually increasing the dose to 2 mg/kg over 5 days. In experimental animals the superior mesenteric artery was clamped for 120 min and then released. Evans blue dye was given intravenously to all animals to quantify pulmonary microvascular injury. Some 60 min after clamp release, the animals were killed and the effects of reperfusion assessed on tissue samples.

Results Evans blue dye concentrations were significantly higher in animals with intestinal ischaemia–reperfusion than in those having sham intestinal ischaemia–reperfusion or in adrenaline-tolerant mice having intestinal ischaemia–reperfusion or sham ischaemia–reperfusion ($P < 0{\cdot}01$). Malonyldialdehyde levels increased significantly in the lung in the intestinal ischaemia–reperfusion group compared with those in the sham ischaemia–reperfusion group ($P < 0{\cdot}001$ for liver, lung and small intestine), whereas there was no difference in adrenaline-tolerant animals. There was no significant change induced by adrenaline tolerance in myeloperoxidase levels in any organ.

Conclusion Adrenaline tolerance reduced the lung permeability caused by intestinal ischaemia–reperfusion. Catecholamines may play a role in free radical generation induced by ischaemia–reperfusion.

The release of catecholamines during various shock states reduces mesenteric vascular perfusion. Resuscitation is accompanied by reperfusion of ischaemic bowel which is thought to cause remote organ injury, especially by neutrophil priming and release of free radicals[1]. In a series of studies it has been shown that adrenaline-tolerant dogs had improved survival from haemorrhagic, endotoxic and cardiogenic shock[2–6]. If adrenaline tolerance is indeed protective in shock states, it may also affect intestinal ischaemia–reperfusion injury by interfering with neutrophil priming or free radical formation. The purpose of this study was to investigate the effect of catecholamine tolerance on organ effects of intestinal ischaemia–reperfusion.

Materials and methods

Swiss albino mice weighing 30–35 g were studied. This experiment was performed in the laboratories of the Departments of Surgical Research and Biochemistry at Hacettepe University Faculty of Medicine. Guidelines for the use and care of laboratory animals were followed. The animals were fed with standard rodent chow and water before and after operation.

Development of adrenaline tolerance

A pilot study was performed to find the LD_{100} (lethal dose at which 100 per cent of animals die) for adrenaline. A single dose of 2 mg/kg was lethal in all of 20 animals studied. This dose was chosen as the target and a novel model for adrenaline tolerance was developed. Briefly, animals were injected with intravenous adrenaline, starting with 0·05 mg/kg which was gradually increased to 2 mg/kg over 5 days. The drug was diluted in 0·4 ml saline. Control animals were injected with an equivalent volume of saline for 5 days.

Induction of intestinal ischaemia–reperfusion

Some 72 h after completion of injections, control animals and adrenaline-tolerant mice were divided into two subgroups: intestinal ischaemia–reperfusion and sham intestinal ischaemia–reperfusion. There were between 11 and 19 animals in each subgroup. Following an overnight fast animals were anaesthetized with ketamine 60 mg/kg and xylazine 4 mg/kg. Evans blue dye (30 mg/kg) was injected intravenously. Following this, laparotomy was performed and the superior mesenteric artery (SMA) was clamped for 120 min with a microclip, followed by a 60-min reperfusion. In the sham ischaemia–reperfusion group the same procedures were performed except for SMA clamping.

Measurement of pulmonary injury

Pulmonary microvascular dysfunction was assessed by measuring the concentration of Evans blue dye within the lung. Evans blue dye binds avidly to albumin and is used as a marker of protein extravasation and inflammatory tissue injury[7,8]. After 60 min of reperfusion the animals were killed and tissues harvested. Pulmonary vessels were emptied of blood by infusing saline into the right ventricle. The lungs were then weighed, placed in 5 ml formamide and homogenized. The tissue suspension was incubated in formamide at 37°C for 16 h, after which the dye concentration was measured by spectrophotometer at 620 nm. The concentration of Evans blue dye extracted from the lungs was expressed in nanograms of dye per milligrams of wet lung weight.

Determination of reperfusion injury

After 60 min of reperfusion a portion of the right lobe of the liver, the left lung and a segment of small intestine were used for

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analysis. Tissue malonyldialdehyde (MDA), an end-product of lipid peroxidation, was measured as a marker of free radical-induced lipid destruction. Tissue myeloperoxidase (MPO) was assessed to determine neutrophil infiltration as a marker of the severity of intestinal ischaemia–reperfusion. MPO and MDA were determined spectrophotometrically according to the methods described by Suzuki *et al.*[9] and Mihara and Uchiyama[10] respectively.

Statistical analysis

One-way analysis of variance was used to assess differences in all data followed by Newman–Keuls *post hoc* analysis. $P < 0{\cdot}05$ was considered significant.

Results

Pulmonary permeability was significantly greater in mice subjected to SMA clamping without previous induction of adrenaline tolerance (mean(s.d.) Evans blue concentration 225·9(45·5), $P < 0{\cdot}01$ *versus* other groups) (*Fig. 1*).

Mean(s.d.) MDA levels were significantly increased in lung (64·9(14·0) nmol/g), liver (57·4(8·5) nmol/g) and small intestine (83·0(15·8) nmol/g) in the intestinal ischaemia–reperfusion group *versus* sham ischaemia–reperfusion animals (46·4(10·1), 42·5(7·1) and 53·6(9·0) nmol/g respectively) ($P < 0{\cdot}001$ for all three organs). Both adrenaline-tolerant groups had significantly higher MDA levels than the sham intestinal ischaemia–reperfusion group ($P < 0{\cdot}005$ for all three organs). In addition MDA levels in the liver of both adrenaline-tolerant groups were significantly higher than in the ischaemia–reperfusion group (*Fig. 2*). There was no significant difference, however, in MDA levels between the two adrenaline-tolerant groups for all organs.

In lung tissue, mean(s.d.) MPO levels were significantly higher in the intestinal ischaemia–reperfusion group (193·2(46·6) units/g) than in the sham ischaemia–reperfusion group (114·2(52·9), $P < 0{\cdot}005$) (*Fig. 3*). Although MPO levels were also higher in liver and intestine in the intestinal ischaemia–reperfusion group, the difference was not significant in, or between, normal or adrenaline-tolerant animals.

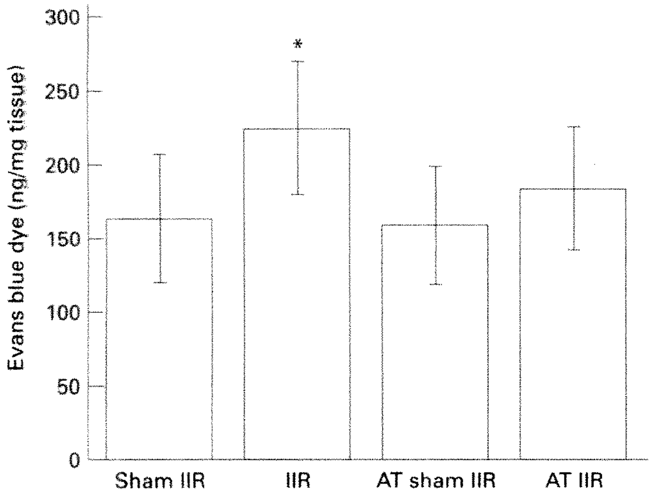

Fig. 1 Comparison of pulmonary permeability. Values are mean(s.d.). IIR, intestinal ischaemia–reperfusion; AT, adrenaline-tolerant mice. $^*P < 0{\cdot}01$ *versus* other groups (analysis of variance followed by Newman-Keuls post-hoc analysis)

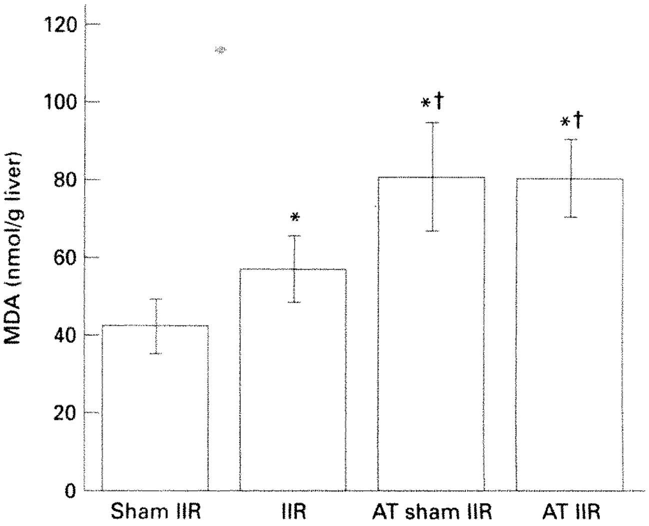

Fig. 2 Comparison of liver malonyldialdehyde (MDA) levels. Values are mean(s.d.). IIR, intestinal ischaemia–reperfusion; AT, adrenaline-tolerant mice. $^*P < 0{\cdot}001$ *versus* sham IIR; $^†P < 0{\cdot}001$ *versus* IIR (analysis of variance followed by Newman-Keuls post-hoc analysis)

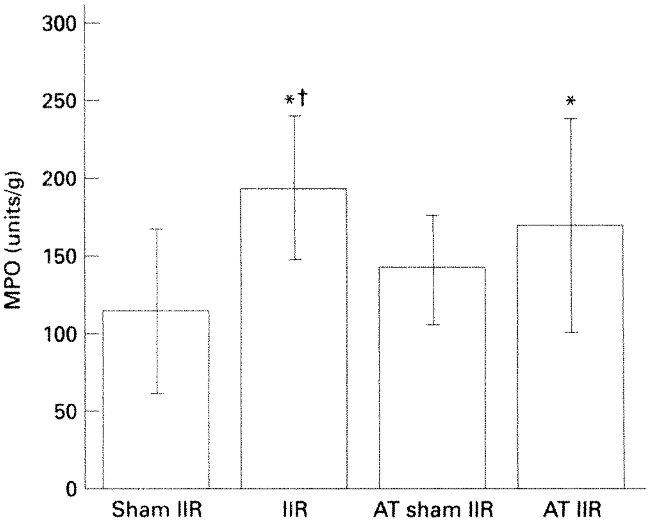

Fig. 3 Comparison of lung myeloperoxidase (MPO) levels. Values are mean(s.d.). IIR, intestinal ischaemia–reperfusion; AT, adrenaline-tolerant mice. $^*P < 0{\cdot}05$ *versus* sham IIR; $^†P < 0{\cdot}05$ *versus* AT sham IIR (analysis of variance followed by Newman-Keuls post-hoc analysis)

Discussion

Adrenaline tolerance can be produced by continued exposure to catecholamines. Various mechanisms cause this phenomenon including a decrease in the avidity of the receptors[11], a decrease in the number of receptors[11–14], an increase in the level of inhibitory G protein α-subunits[13] or a decrease in catecholamine-induced adenyl cyclase activity[12,13]. Tolerance to both α_1- and α_2-adrenergic receptor-mediated vasopressor responses in rats with transplanted phaeochromocytoma tumours can be demonstrated[15]. In patients with a phaeochromocytoma, the density of α and β adrenoceptors is decreased. This returns to normal 3 months after surgery[16].

Previous studies on adrenaline tolerance were performed on dogs. Tolerance was developed by administering intravenous adrenaline every 2–3 days for a few weeks[3]. In this study the drug was given for 5 days because gradual sclerosis of the tail skin or tail vein occurred, due to small amounts of extravasated adrenaline. The mortality rate was approximately 75 per cent by the end of 7 days. Most of the deaths occurred after the first two doses.

Ischaemia–reperfusion is associated with raised catecholamine levels caused by impairment of uptake and storage[17]. Intestinal ischaemia–reperfusion causes pulmonary vasoconstriction[18] and liver ischaemia, and is accompanied by increased catecholamine levels and pulmonary hypertension[19]. It is known that pulmonary hypertension leads to accumulation of interstitial lung water by increasing microvascular filtration pressure[20]. In the present model, decreased pulmonary permeability could be the result of an attenuated catecholamine effect.

Increased lipid peroxidation in lung, liver and small intestine in animals with intestinal ischaemia–reperfusion was evidenced by significantly increased MDA levels in all three organs. This has been demonstrated previously in different studies with significantly increased MDA levels in lung[21], and intestine[22] induced by intestinal ischaemia–reperfusion. Conversely, there was no difference in MDA levels in adrenaline-tolerant animals having intestinal ischaemia–reperfusion or sham ischaemia–reperfusion. However, MDA levels in the sham adrenaline-tolerant group were significantly higher than in the sham ischaemia-reperfusion animals. Two mechanisms might have contributed to this result. One might be ischaemic vasoconstruction and reperfusion due to the adrenaline injections, contributing to increased MDA levels. The other might be the oxidation products of adrenaline, which is known to generate free oxygen radicals[23,24].

One study[25] showed that after induction of ischaemia, inhibition of monoamine oxidase attenuates production of hydrogen peroxide, revealing the importance of catecholamine oxidation in ischaemia–reperfusion injury. In the liver, the difference between MDA levels in normal and adrenaline-tolerant animals was more evident, as both adrenaline-tolerant groups had significantly higher MDA levels than the intestinal ischaemia–reperfusion group. This might be because catecholamines are mostly metabolized in liver and monoamine oxidase has its highest concentrations in liver and kidney[26]. These findings support the hypothesis that oxidation of catecholamines leads to accumulation of oxygen free radicals.

The second result is the attenuation of intestinal ischaemia–reperfusion-induced lipid peroxidation by adrenaline tolerance. There was no significant difference between the two adrenaline-tolerant groups, showing that the intestinal ischaemia–reperfusion insult did not lead to additional lipid peroxidation. This suggests that catecholamines are involved in ischaemia–reperfusion injury, possibly having a positive modulatory role. Some reports have shown an association of catechol adrenergic agents with the xanthine oxidase system[27,28], suggesting the latter has a catalytic role for catechol adrenergic agents on xanthine oxidase. Ischaemic preconditioning might be another explanation for the protective effect of adrenaline tolerance.

MPO levels increase in lung[29,30] and intestine[22,29,30] during intestinal ischaemia–reperfusion, and act as a marker for neutrophil infiltration. In the present study, MPO levels were also increased by intestinal ischaemia–reperfusion in all three organs studied, although significantly only in the lung. In this model, adrenaline tolerance did not have any effect on intestinal ischaemia–reperfusion-induced changes in MPO levels in any organ. Catecholamines may not play a major role in neutrophil activation.

The present study indicates that catecholamines are involved in intestinal ischaemic injury and that induction of adrenaline tolerance has a possible protective role.

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Prospective analysis of quality of life in patients following infrainguinal reconstruction for chronic critical ischaemia

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Background The aims of this prospective study were to analyse the health-related quality of life (QOL) changes associated with infrainguinal arterial reconstruction for chronic critical limb ischaemia (CLI) and to assess the impact of graft patency and limb salvage.

Methods Fifty-five consecutive patients, 28 women and 27 men of median age 71 (range 41–86) years, undergoing infrainguinal arterial reconstruction for CLI, consented to participate in the study. QOL was assessed using the Short Form 36 (SF36) health survey questionnaire, which was completed before and at 1, 3, 6 and 12 months following surgery. Graft patency was assessed by duplex imaging at the same postoperative intervals.

Results CLI severely impaired QOL. Cumulative graft patency at 1, 3, 6 and 12 months after surgery was 82, 78, 76 and 64 per cent respectively. Reconstruction resulted in significant improvements in the SF36 domains Physical Functioning, Pain, Vitality and Social Functioning ($P < 0{\cdot}01$). With a patent graft these improvements began soon after surgery and were maintained for the 12 months studied. Following irredeemable graft occlusion, patients who had secondary amputation also described some QOL improvements.

Conclusion A patent graft following infrainguinal arterial reconstruction for critical ischaemia results in an immediate and lasting improvement in health-related QOL.

The incidence of chronic critical limb ischaemia (CLI) is estimated at 50–100 per 100 000 population per year[1]. Reconstructive arterial surgery is increasing[2–4]. Compared with amputees, patients who undergo revascularization are less likely to die or need long-term institutional care, are more likely to have a short hospital stay, to be discharged home and to survive longer once discharged[4–6]. Successful revascularization is more cost effective than amputation[7]. Despite these advantages there is little information available concerning the impact of vascular reconstruction on the quality of life (QOL). Previously, domain-specific questionnaires have been used which make comparisons difficult and no information is given regarding QOL before intervention. Conclusions regarding QOL benefits following vascular reconstruction are difficult to make[8,9]. Early postoperative QOL assessment is essential to ensure that the impact of postoperative recovery and complications is not overlooked[10,11]. The mortality rate of patients with chronic critical ischaemia is 10–20 per cent per annum; it is therefore important that the functional outcome of patients who die in the early postoperative period is documented as fully as possible. Sequential postoperative assessments are preferable in order to identify trends in QOL[12]. The aim of this prospective observational study was to analyse the impact of infrainguinal arterial reconstruction for critical ischaemia on patient-reported QOL and to assess the effect of graft patency and limb salvage.

Patients and methods

Over 6 months, 65 consecutive patients with CLI according to International Society for Cardiovascular Surgery (ISCVS) criteria[13], listed for infrainguinal arterial reconstruction, were invited to participate in the study. Fifty-five patients consented and were studied prospectively. Graft patency was assessed at 1, 3, 6 and 12 months following surgery by duplex imaging.

Patients' QOL was assessed using the Short Form 36 (SF36) before and at 1, 3, 6 and 12 months after surgery. The SF36 was developed from the Medical Outcomes Study questionnaire in the USA. In this study the UK version was used. The SF36 contains 36 items which measure eight QOL dimensions or domains: Physical Functioning, Role limitation due to Physical problems (Role Physical), Social Functioning, Role limitations due to Emotional problems (Role Emotional), Mental Health, Vitality, Pain and General Health. Item scores for each domain are coded, summed and transformed on to a scale from 0 (worst possible score) to 100 (best possible score). The SF36 is the product of a vast amount of developmental work and psychometric testing in the USA[14–18].

Data were collected on a Microsoft Access database and analysed using a Microsoft (Wokingham, UK) Excel spreadsheet with Astute (University of Leeds, UK) Statistical Analysis software. QOL scores were not normally distributed (Kolmogorov–Smirnov goodness of fit test). QOL scores for the whole group are presented as median values and Kruskal–Wallis one-way analysis of variance was used to assess significant changes.

Subgroup QOL analysis, based on graft patency, is presented as effect sizes, and in this case the Mann–Whitney U test was used for comparison with pretreatment values. Effect sizes were calculated by dividing the difference between the pretreatment and post-treatment median values by the interquartile range of the pretreatment values[19].

Subgroup QOL analysis 12 months after intervention, based on graft patency and limb salvage, is presented as standard scores.

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Only at 12 months did each subgroup contain sufficient patients for meaningful comparison. Standard scores were calculated by dividing the differences between the median scores of each subgroup and those of the general population by the interquartile range of the general population[20,21].

Results

The 55 patients studied, 28 women and 27 men of median age 71 (range 41–86) years, reported a median symptom duration of 12 months (range 2 months to 30 years). The incidence of co-morbidity and predisposing factors according to reporting standards recommended by the ISCVS is shown in *Table 1*[13]. Previous ipsilateral interventions included 15 infrainguinal bypass procedures, three superficial femoral artery percutaneous transluminal angioplasties (PTAs) and five suprainguinal inflow procedures. Previous contralateral interventions included six infrainguinal bypass procedures, one superficial femoral artery PTA and four amputations. Nineteen patients had rest pain and 36 had tissue necrosis. Nineteen patients underwent a femoropopliteal (six above knee, 13 below knee) bypass graft, 33 a femorocrural (13 anterior tibial, ten posterior tibial, ten peroneal) bypass graft and three a femorodorsalis pedis graft. Long saphenous vein (LSV) alone was used in 22 patients (five *in situ*, 17 reversed grafts), a combination of LSV and arm vein in eight, externally supported polytetrafluoroethylene (PTFE) with vein cuff in 20, and composite PTFE and vein graft in five.

The ten patients, seven men and three women, who declined to participate were significantly older than those in the study group (median age 75 (range 71–90) years) ($P = 0{\cdot}01$, Mann–Whitney U test), but were otherwise similar to the study group in terms of sex, co-morbidity, factors predisposing to peripheral vascular disease, severity of lower limb ischaemia, previous ipsilateral or contralateral interventions, and QOL before intervention. Cumulative graft patency was 82, 78, 76 and 64 per cent at 1, 3, 6 and 12 months after surgery respectively[13] (*Table 2*). Four of the 11 patients who had secondary amputation were completely wheelchair-dependent at 12 months.

Infrainguinal arterial reconstruction significantly improved SF36-measured Physical Functioning, Pain, Vitality and Social Functioning scores (*Fig. 1*). There were no significant improvements in the SF36 domains of Role Physical, General Health, Role Emotional or Mental Health following reconstruction. Subgroup analysis according to graft patency (*Fig. 2*) demonstrated that a patent graft results in an immediate improvement in Physical Functioning, Role Physical, Pain and Social Functioning, which are maintained for up to 12 months. A delayed improvement in Vitality was observed in patients with a patent graft at 6 and 12 months. The only QOL domains that improved following graft occlusion were Pain, Vitality and Social Functioning at 6 months. No significant improvements in Physical Functioning and Role Physical were detected at any of the follow-up assessments if graft occlusion had occurred (*Fig. 2*). Graft patency had no influence on General Health, Role Emotional or Mental Health dimensions.

Subgroup QOL analysis based on graft patency and limb salvage at 12 months after intervention (*Fig. 3*) demonstrated that patients with a patent graft were the only subgroup to gain any benefit in the SF36 domains of Physical Functioning and Role Physical, but did not quite attain the values of a matched normal population (standard score below zero). Patients with an occluded graft, irrespective of whether amputation was needed, had little or no change from pretreatment scores in these two domains at 12 months, with scores inferior to a matched population (standard score less than − 1). Patients with a patent graft and those who required secondary amputation had similar improvements in the domains of

Table 1 Predisposing factors and co-morbidity

Condition	No. of patients
Diabetes	
None	38
Adult onset, drug controlled	8
Adult onset, insulin controlled	8
Juvenile onset	1
Hypertension	
None	35
Controlled, one drug	10
Controlled, two drugs	9
Uncontrolled, more than two drugs	1
Smoking	
Never/ > 10 years' abstinence	17
Abstinence < 10 years	12
Abstinence < 1 year/ < 20 per day	22
> 20 per day	4
Ischaemic heart disease	
Asymptomatic/normal ECG	27
Remote MI	8
Stable angina, atrial fibrillation, controlled CCF	19
Unstable angina, symptomatic arrhythmia, poorly controlled CCF, recent MI	1
Cerebrovascular disease	
Asymptomatic, no bruit	45
Asymptomatic, with bruit	2
Transient/temporary stroke	4
Stroke with permanent deficit	4
Hyperlipidaemia	
Normal blood lipids	43
Mild increase, diet controlled	6
Strict diet control	2
Drug controlled	4

ECG, electrocardiogram; MI, myocardial infarction; CCF, congestive cardiac failure

Table 2 Life table analysis of survival and graft patency

	Time after surgery (months)			
	1	3	6	12
No. of patent grafts	38	35	31	26
Primary	32	29	25	22
Primary assisted	5	4	3	3
Secondary	1	2	3	1
Graft occlusions	9	11	12	17
Limb salvaged	1	3	3	6
Secondary amputation	8	8	9	11
Not available for follow-up	8	9	12	12
Died	5	5	7	7
Lost/withdrawn	3	4	5	5
Interval patency rate	0·82	0·95	0·97	0·83
Cumulative patency rate (%)	82	78	76	64
Standard error (%)	4·7	5·9	6·3	6·9

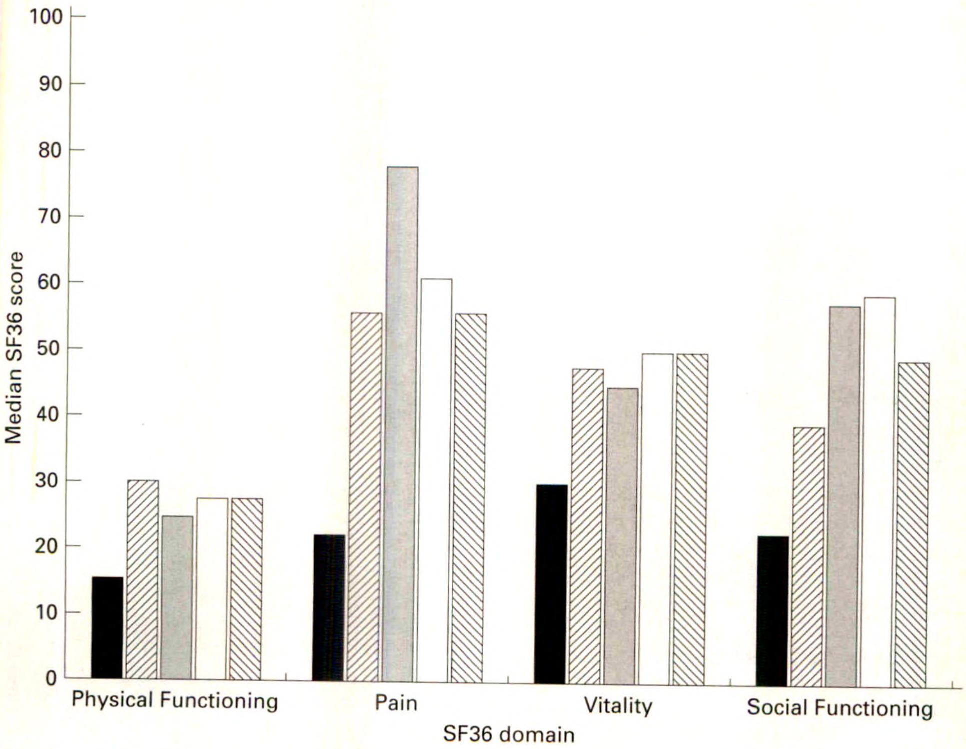

Fig. 1 SF36 results for all patients irrespective of graft patency before (■) and 1 month (▨), 3 months (▩), 6 months (□) and 12 months (▧) after operation. $P < 0{\cdot}01$ for all domains shown; there was no significant change for the domains Role Physical, General Health, Role Emotional or Mental Health (Kruskal–Wallis analysis of variance)

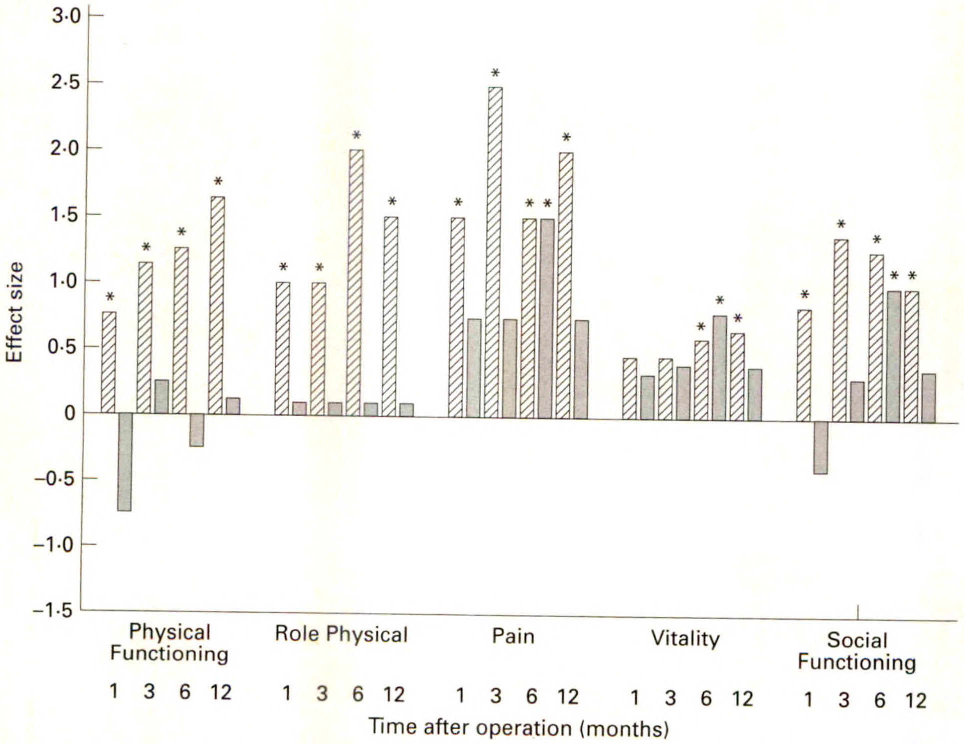

Fig. 2 Effect sizes for patent (▨) and non-patent (▩) grafts. $^*P < 0{\cdot}01$ *versus* pretreatment value (Mann–Whitney *U* test)

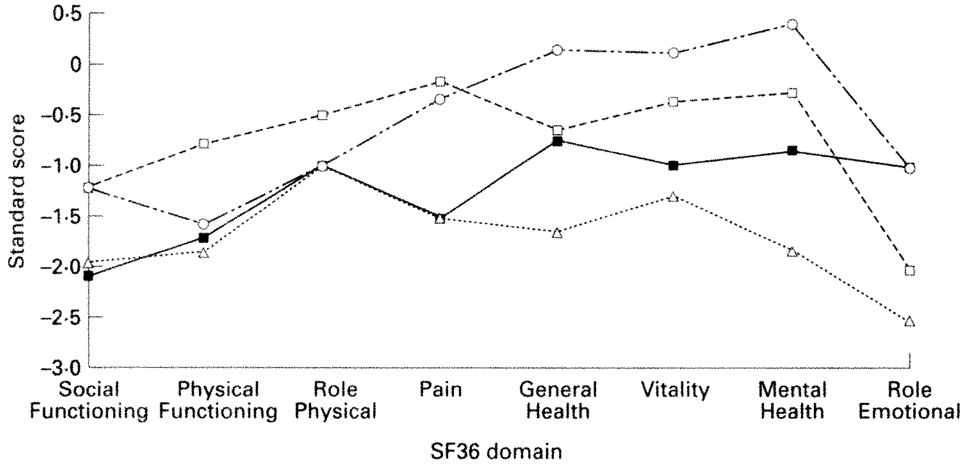

Fig. 3 Standard SF36 scores before intervention (■) and 12 months following intervention according to outcome: patent graft (□); occluded graft — leg not amputated (△); or occluded graft — leg amputated (○)

Pain, Vitality, Mental Health and Social Functioning, with standard scores in the first three domains approaching those of a matched population. In several of the psychological domains (e.g. General Health, Vitality, Role Emotional and Mental Health) the standard scores for secondary amputees were superior to those in patients with a patent graft. Patients with a non-redeemable occluded graft who declined amputation, although few in number, seemed to return to the dismal QOL experienced before intervention, and demonstrated further deterioration in many of the psychological domains. This group of patients had the lowest QOL score in virtually all of the SF36 domains, with scores falling way below those of a matched population (standard score less than − 1·5).

Discussion

A 12-month cumulative patency rate of 64 per cent concurs with previous studies, given that 27 per cent of procedures were secondary, sufficient LSV was available in only 40 per cent of patients and 65 per cent had tissue necrosis before surgery[22]. A 1-year mortality rate and overall loss to follow-up, including these deaths, of 13 and 22 per cent respectively matches other studies[23,24]. This relatively large loss remains a major problem when studying patients with CLI and is one of the weaknesses of this study. Frequent sequential assessments were done to try to avoid the omission of QOL data in potentially the sickest patients; however, these are the patients often lost to follow-up and the SF36 results are biased by their omission.

The SF36 is the most appropriate generic health-related QOL assessment for use in patients with CLI[18,25]. Other studies have demonstrated QOL improvements with other instruments[26,27]. CLI has a profoundly detrimental effect on health-related QOL when compared with age-matched population norms[16,20] and other common clinical conditions encountered in the National Health Service[21].

This study demonstrated that successful reconstruction results in almost immediate QOL improvements. However, it can take time to recover fully from surgery, with patients with patent grafts demonstrating continuing improvements in several QOL domains (e.g. Physical Functioning) for up to 12 months following surgery. Significant improvements in some domains (e.g. Vitality) were not evident until 6 months after surgery. Early measurement of QOL is essential and patients should be encouraged to continue to attend for further follow-up. A patent graft has a profound, immediate and lasting impact on QOL which justifies the time and expense associated with these procedures and in the maintenance of graft patency. Although the number of patients with a non-salvageable failed graft is small, this study indicates that a secondary amputation results in severe and lasting limitations to physical activities despite relatively good rehabilitation rates, but improves pain and many of the psychological QOL domains. Potential explanations for the psychological benefits demonstrated in amputees at 12 months may include relief from the ongoing problems of recurrent limb ischaemia and the realization that the daunting problem of life as an amputee can be addressed and overcome. The severe QOL impairment in patients with a failed graft who do not accept amputation may be expected as they not only suffer recurrent CLI but have undergone major surgery in vain.

This study supplies evidence to support an aggressive approach to surgical reconstruction in patients with CLI. Following surgery QOL improvements are observed as long as the graft remains patent. Secondary amputation following non-redeemable graft occlusion also seems to have some QOL benefits.

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Ward *versus* intensive care management of high-risk surgical patients

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Background Selection of high-risk surgical patients for preoperative and perioperative admission to an intensive therapy unit (ITU) for enhancement of oxygen delivery may reduce postoperative morbidity and mortality rates. Limited resources may prevent admission of all suitable patients. This audit study examined whether it is possible to select patients most at risk and thus reduce surgical morbidity and mortality rates when ITU services are limited.

Methods This was a retrospective audit comparing the actual outcomes of complications and death with predicted outcomes using the POSSUM socre (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) for 101 general surgical and vascular patients who would have fulfilled previously suggested criteria for preoperative admission to the ITU. Main outcome measures were the number of preoperative ITU admission criteria, American Society of Anesthesiologists (ASA) and POSSUM scores, preoperative oxygen delivery values, intravenous fluid therapy, length of ITU stay, length of hospital stay, postoperative complications and 28-day mortality.

Results Medical staff allocated patients appropriately. There was a lower mortality rate than predicted from individual POSSUM scores. Patients who were admitted to the ITU before operation had the highest ASA scores, admission criteria and POSSUM scores; they also had significantly lower mortality and morbidity rates than predicted by the POSSUM scoring system.

Conclusion Patients with the greatest reduction in mortality and morbidity rates were admitted to the ITU before operation and had cardiovascular physiology 'optimized' before surgery.

Goal-oriented haemodynamic therapy may reduce mortality in patients at high perioperative risk[1–8]. In 1992 this institution introduced a goal-directed protocol for perioperative enhancement of oxygen delivery for patients at high risk of complications and death after various surgical procedures. This followed a randomized prospective study[1] that had shown a clear benefit of perioperative enhancement of oxygen delivery of patients to the indices suggested by Shoemaker *et al.*[7]. The protocol required admission of all patients expected to be at high postoperative risk to the intensive therapy unit (ITU) before operation (*Table 1*). In the ITU these patients had cardiovascular physiology enhanced by means of specific treatment guidelines suggested by Shoemaker *et al.*[7] and Boyd *et al.*[1]. When the defined treatment goals had been achieved, the patients went to theatre for surgery, returning to the ITU afterwards.

A retrospective study of a 3-month period was conducted, 2 years after the introduction of goal-oriented perioperative enhancement. Owing to lack of ITU beds not all the patients who fulfilled one or more of the criteria for preoperative ITU admission were able to be treated in this fashion.

The purpose of this study was to answer the following three questions. Were medical staff selecting the most appropriate patients for the limited ITU facilities? When patients had been selected for perioperative oxygen enhancement, were they being treated appropriately and correctly? Does ITU management improve the outcome measures of morbidity and mortality in these patients when compared with a previously documented and established database of similarly ill patients?

Patients and methods

Hospital theatre records were reviewed and a list was compile of all general surgical and vascular patients who had had a operation lasting longer than 90 min or who were over 70 year old and having a major operative procedure during a 3-mont winter period from December to February. All patient note were reviewed to determine whether they fulfilled the criteria fo perioperative enhancement of oxygen delivery (*Table 1*). If the

Table 1 Shoemaker–Boyd entry criteria*

Any patient whose operation is planned to exceed 90 min and who has one or more of the following:

1. Previous severe cardiorespiratory illness with current reduced cardiorespiratory reserve (e.g. acute myocardial infarction, chronic obstructive pulmonary disease, cerebrovascular accident)
2. Respiratory failure (P_{aO_2} less than 6 kPa or F_{iO_2} greater than 0·4 or currently requiring mechanical ventilation)
3. Shock (mean arterial pressure less than 60 mmHg, central venous pressure lower than 15 mmHg, urine output less than 20 ml h^{-1}, cold and clammy)
4. Acute abdominal catastrophe with haemodynamic instability
5. Massive blood loss (more than 8 units)
6. Age over 70 years *and* evidence of significantly reduced physiological reserve in one or more organs
7. Acute renal failure (urea greater than 20 mmol l^{-1}, creatinine greater than 260 mmol l^{-1}) of sudden recent onset
8. Planned extensive ablative surgery for carcinoma (e.g. gastrectomy, oesophagectomy)
9. Late-stage vascular disease associated with aortic disease

*Criteria suggesting that a patient may benefit from admission to an intensive therapy unit before operation for cardiovascular augmentation and pharmacological enhancement of physiology to achieve a tissue oxygen delivery of at least 600 ml min^{-1} m^{-2} body surface area before surgery[1,7]. P_{aO_2}, arterial partial pressure of oxygen; F_{iO_2}, fraction of inspired oxygen

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did, they were included in the audit. The outcome of these patients following operation was analysed retrospectively. Actual outcome was compared against predicted outcome using a surgical scoring system to evaluate the severity of illness for individual patients and to compare the outcome of individual patients against an established database of similar patients in other hospitals in the UK. This scoring system, the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM), devised by Copeland *et al.*[9], has been well evaluated for surgical audit and allows a predicted morbidity and mortality risk to be calculated for each patient. POSSUM has been used for general and vascular surgery audit[10,11]. It has been shown to give a better prediction of outcome for surgical patients than Acute Physiology And Chronic Health Evaluation (APACHE) II[12] (a scoring system for recording both acute physiological status and chronic health changes in the first 24 h after admission to an ITU).

Patients who fulfilled the criteria were separated into three groups based on the time of admission to the ITU: (1) no admission to the ITU, (2) admission to the ITU after operation, and (3) admission to the ITU before operation. The following data were collected: type of operation carried out, age, weight, all perioperative indices of cardiovascular performance, perioperative fluids, postoperative complications or death within 28 days of operation, length of ITU stay, duration of hospital stay, and American Society of Anesthesiologists (ASA) and POSSUM scores.

The ASA score[13] is a five-point assessment of preoperative physical status devised to classify patients into grades according to their preoperative general medical condition. POSSUM takes into account the following patient-derived data: age, cardiac signs, chest radiograph, respiratory history, blood pressure, heart rate, Glasgow Coma Score, haemoglobin level, white cell count, plasma urea, sodium and potassium concentrations, and the electrocardiogram. Each item in the score is graded and the patient is awarded 1, 2, 4 or 8 points for increasing derangement. The minimum score is 12 and the maximum 120. Scoring is carried out immediately before operation but after resuscitation has taken place, thus avoiding the complication of lead-time bias[14,15]. Included in POSSUM is the Operative Severity Score (OSS), which is taken after (and is dependent on) the surgical procedure performed[9]. Using POSSUM it is possible to predict morbidity and mortality risk for a particular patient based on the outcome of similar patients in the POSSUM database. Prediction of morbidity and mortality was made for the patients in this audit and compared against actual outcome.

Furthermore, to attempt to identify whether there were specific groups of patients who might be either at risk from treatment or potentially able to benefit from it, three groups were subdivided into patients with a predicted morbidity or mortality rate of 50 per cent or less ('low risk') and those with a predicted morbidity or mortality rate of 51 per cent or more ('high risk').

Patients admitted to the ITU before operation were treated according to established protocols based on a previous study[1] of perioperative oxygen enhancement. Initial treatment involved supplemental oxygen (where appropriate), intravenous fluids and/or intravenous blood products if required. The immediate aims were to achieve arterial oxygen saturation of over 94 per cent, pulmonary arterial occlusion pressure of between 12 and 14 mmHg, haemoglobin concentration greater than $12\ \mathrm{g\ dl^{-1}}$, mean arterial pressure of 80–110 mmHg and urine output of over $0{\cdot}5\ \mathrm{ml\ kg^{-1}\ h^{-1}}$. After this initial treatment the cardiac index was measured and oxygen delivery index (DO_2I) was calculated. If this was less than $600\ \mathrm{ml\ min^{-1}\ m^{-2}}$ body surface area, an intravenous inotrope or vasodilator was commenced. The dose was doubled every 30 min until a DO_2I of $600\ \mathrm{ml\ min^{-1}\ m^{-2}}$ was achieved or side-effects were noted. The endpoint of a DO_2I of $600\ \mathrm{ml\ min^{-1}\ m^{-2}}$ for inotrope and/or vasodilator therapy was chosen because this was the median value noted for survivors by Bland *et al.*[2].

Postoperative complications were recorded retrospectively and were defined as in Boyd *et al.*[1] by specific diagnostic criteria.

Statistical analysis

Data are presented as mean(s.e.m.) or median, and were compared with a paired t test, the Mann–Whitney U test or Fisher's exact test as appropriate using the GraphPad Prism (v2.0) program for Apple Macintosh (GraphPad Software, San Diego, California, USA). A significant difference was assumed if $P < 0{\cdot}05$.

Results

In all, 129 patients' notes were reviewed. Of these, 28 patients did not fulfil the criteria required for preoperative admission to the ITU and their notes were not studied further. Some 101 patients fulfilled the entry criteria for perioperative intensive care and goal-oriented haemodynamic therapy. Of these, 40 (40 per cent) went to the ITU before operation, 31 (31 per cent) went to the ITU after operation, and 30 (30 per cent) did not go the ITU at all. The case mix for all three groups was two-thirds general surgical and one-third vascular surgery. The age of the patients was similar in all three groups (*Table 2*).

It can be seen that the number of Shoemaker–Boyd criteria[1,7] used for entry to this study increased between the three groups. Patients not admitted to the ITU had the lowest mean number of criteria, and those with the greatest mean number were admitted to the ITU before operation. Patients who were admitted to the ITU after

Table 2 Numbers of patients, admission criteria, physiological and operative scores and emergency cases, grouped by timing of admission to the intensive therapy unit

	No ITU	ITU after operation	ITU before operation
No. of patients	30	31	40
Mean(s.e.m.) age (years)	71·6(2·9)	69·3(2·9)	72·2(1·9)
No. of admission criteria			
Median	1	2*	2†
25th percentile	1	1	2
75th percentile	2	2	3
Range	1–3	1–3	1–3
ASA score			
Median	3	3‡	4†
25th percentile	2	2	3
75th percentile	3	3	4
Range	2–4	1–4	2–4
POSSUM			
Median	22	26#§	36†
25th percentile	19	20	29
75th percentile	36	40	51
Range	15–36	12–40	13–51
OSS			
Median	14	18¶	18**
25th percentile	11	15	15
75th percentile	16	23	22
Range	8–25	8–28	12–29
Emergency operation	13	15	29

ITU, intensive therapy unit; ASA, American Society of Anesthesiologists; POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity; OSS, Operative Severity Score. *$P = 0{\cdot}011$, ‡$P = 0{\cdot}0019$, #$P = 0{\cdot}0015$ (ITU after *versus* ITU before operation); †$P < 0{\cdot}0001$, **$P < 0{\cdot}0005$ (ITU before operation *versus* no ITU); §$P = 0{\cdot}027$, ¶$P = 0{\cdot}001$ (ITU after operation *versus* no ITU) (Mann–Whitney U test) operation had an intermediate number of criteria. Likewise, there was an increase in ASA and POSSUM scores between patients not going to the ITU before operation (*Table 2*). These differences were significant. However, there was no significant difference in OSS (representing the complexity of the operation) between groups going to the ITU, although the group of patients who did not go to the ITU had less complex operations as scored by the OSS. The proportion of cases admitted as emergencies was highest in the group that went to the ITU before operation.

Table 3 shows duration of ITU and hospital stay as well as the volume of intravenous fluid given before operation and that given during the 24 h from the start of operation. Median duration of ITU stay was nearly twice as long in those who were admitted to the ITU before operation compared with those who were admitted only once the operation had been performed. However, it can be seen from the range of ITU stay that postoperative stay was very variable. Although the time spent in the ITU includes time before operation, it does not include operating time. However, it is difficult to determine the actual time taken for preoperative enhancement because some elective patients were admitted the evening before operation and remained in the ITU overnight even though physiological cardiovascular enhancement may have taken place several hours earlier. In view of this and the very wide range of ITU stay it was not deemed appropriate to apply any form of statistical testing to the data on ITU stay. After operation, the length of hospital stay did not alter significantly between the groups. Patients with prolonged postoperative hospital stay were confined to the two groups admitted to the ITU either before or after operation.

Table 3 Numbers of patients, duration of intensive care and hospital stay, intravenous fluid therapy, complications and 28-day postoperative mortality, grouped by timing of admission to the intensive therapy unit

	No ITU	ITU after operation	ITU before operation
No. of patients	30	31	40
ITU stay (h)			
Median	0	26	48
25th percentile	0	24	39
75th percentile	0	52	96
Range	0	1–336	12–1224
Hospital stay (days)			
Median	17	21	19
25th percentile	12	11	14
75th percentile	33	28	41
Range	2–49	1–121	2–97
Preop. intravenous fluid (ml)			
Median	0	900	1075
25th percentile	0	0	562
75th percentile	1000	2000	1500
Range	0–4500	0–6000	0–6825
24-h periop. intravenous fluid (ml)			
Median	4800	7650	4650
25th percentile	3950	5763	3225
75th percentile	6150	10640	6300
Range	1600–7100	2900–22400	2200–17700
Postoperative complications	13	26	28
Mortality at 28 days	2	7	12

ITU, intensive therapy unit

Preoperative fluid management also differed between the groups, with the group that went to ITU before operation receiving most. Both other groups received intravenous fluids before operation, those going to the ITU after surgery receiving the greatest amount. However, it can be seen that intravenous fluid given to all three groups in the perioperative 24 h was similar, with patients going to the ITU after operation receiving slightly more than those in the other two groups. Despite the large amount of intravenous fluid administered during this perioperative phase (more than 20 litres in some cases) there was no recorded case of cardiac failure or pulmonary oedema as a consequence of intravenous fluid overload. It should be noted that all patients who were admitted to the ITU (both before and after operation) had intravascular fluid status monitored with a pulmonary artery flotation catheter.

The OSS for the two groups of patients admitted to the ITU was similar. The numbers of recorded complications rose in parallel with the numbers of admission criteria, ASA and POSSUM scores. Patients who were not admitted to the ITU had a lower number of complications, with only 13 of 30 being recorded as having defined postoperative complications, than the sicker patients with the higher POSSUM scores who went to the ITU both before and after operation. Patients who were admitted to the ITU after surgery had the largest number of complications (26 of 31 patients) despite being significantly fitter physiologically before operation than those who went to the ITU before operation.

Mortality at 28 days after operation reflects the increasing illness and operative complexity of the three groups: only two of 30 patients who did not go to the ITU had died, compared with seven of 31, of those who went to the ITU after operation and 12 of 40 who went to the ITU before operation.

Using POSSUM and OSS for these patients, a comparison could be made between the three groups for predicted and actual 28-day mortality and morbidity rates. The POSSUM-predicted mortality rate was 19 per cent for patients who did not go to the ITU, 37 per cent for those who went to the ITU after operation and 57 per cent for those who went to the ITU before operation. The actual mortality rates were consistently lower (*Table 4*). In the group who went to the ITU before operation the

Table 4 Actual and predicted 28-day mortality and morbidity rates grouped by timing of admission to the intensive care unit

	No ITU ($n = 30$)	ITU after operation ($n = 31$)	ITU before operation ($n = 40$)
Mortality rate (%)			
Actual*	7	23	30‡
Predicted	19	37	57
Morbidity rate (%)			
Actual†	67	84	70§
Predicted	58	75	90

*Actual no. of patients alive at 28 days was 28, 24 and 28 respectively for no intensive therapy unit (ITU) admission, ITU after operation and ITU before operation; †actual no. of patients with postoperative complications was 20, 26 and 28 respectively. ‡$P = 0{\cdot}024$, §$P = 0{\cdot}048$ (actual *versus* predicted value, Fisher's exact test) reduction in mortality rate from that predicted was significant ($P = 0{\cdot}024$).

Similarly the complication rate seen in the patients admitted to the ITU before operation was lower than that expected (72 *versus* 90 per cent, $P = 0{\cdot}048$). However, for patients admitted to the ITU after operation or not admitted to the ITU at all, there was a slightly higher complication rate than that predicted (*Table 4*).

To determine which patients obtained benefit from the ITU each of the three groups was divided into two subgroups, 'high' and 'low' risk, based on the POSSUM-predicted outcome. In the high risk groups (51–100 per cent predicted risk) there was a significant reduction in mortality rate in patients who were admitted to the ITU before operation (*Table 5*). The POSSUM-predicted mortality rate for this group was 77 per cent but the actual mortality rate was only 32 per cent. In the groups predicted to have a greater than 50 per cent likelihood of postoperative complications, only patients admitted to the ITU before operation had fewer complications than predicted.

In the subgroups designated as at 'low risk' (i.e. less than 50 per cent risk of death or complications) there was no significant difference between predicted and actual outcome. The predicted mortality rate in the low-risk patients having preoperative care was 28 per cent, but four of 15 (27 per cent) patients actually died.

Table 6 shows the features of 40 patients who were admitted to ITU before operation. These patients have been divided into two groups depending on whether or not they achieved the target of tissue oxygen delivery of equal to or greater than 600 ml kg^{-1} mg^{-2} body surface area.

Fourteen patients achieved a tissue oxygen delivery of equal to or greater than 600 ml kg^{-1} m^{-2} body surface area before being transferred to the operating theatre. The other 26 patients did not achieve this goal. These latter patients had a slightly higher POSSUM but slightly lower OSS. The group of patients who did not achieve a DO_2I greater than 600 ml kg^{-1} m^{-2} were older and included a slightly greater proportion of emergency patients. In effect this group was older and more frail, with less cardiovascular and respiratory reserve.

Both groups of patients had a resting DO_2I of less than 600 ml kg^{-1} m^{-2} and in both there was an increased DO_2I before operation. Neither group showed any significant increase in heart rate before operation and the median volume of intravenous fluid given to both groups before surgery was similar. The postoperative ITU stay of the two groups was the same but there was a large range. Postoperative hospital stay was shorter in patients who did not achieve a DO_2I greater than 600 ml kg^{-1} m^{-2} but the range in both groups was very wide. The postoperative complication rate in the two groups was similar at 64 and

Table 5 Predicted and actual mortality and complication rates in high-risk patients*

	No ITU	ITU after operation	ITU before operation
Actual mortality	0 of 2 (0)	4 of 10 (40)	8 of 25 (32)†
POSSUM-predicted mortality	1·2 of 2 (60)	7·5 of 10 (75)	19·2 of 25 (77)
Actual complications	13 of 14 (93)	22 of 23 (96)	27 of 39 (69)‡
POSSUM-predicted morbidity	10·2 of 14 (73)	19·8 of 23 (86)	36·5 of 39 (94)

*Predicted risk of complication or death greater than 50 per cent. ITU, intensive therapy unit; POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. †$P = 0{\cdot}0041$, ‡$P = 0{\cdot}0063$ (actual *versus* predicted value, Fisher's exact test)

Table 6 Data for 40 patients admitted to the intensive therapy unit before operation, divided into subgroups based on whether target tissue oxygen delivery was achieved before operation and general anaesthesia

	Achieved DO_2I of >600 ml min^{-1} m^{-2}	Failed to achieve DO_2I of >600 ml min^{-1} m^{-2}
No. of patients*	14 (35)	26 (65)
Median (range) no. of admission criteria	2 (1–3)	2 (1–3)
Median (range) ASA score	4 (2–4)	4 (2–4)
Median (range) POSSUM	31·5 (13–58)	37 (17–51)
Median (range) OSS	19·5 (10–33)	18 (8–26)
No. of emergency patients*	8 (57)	20 (77)
Mean(s.e.m.) (range) (years)	68·5(4·4) (29–86)	74·2(1·7) (55–86)
Mean(s.e.m.) (range) admission DO_2I (ml min^{-1} m^{-2})	455(40·4) (272–656)	376(22·9) (100–565)
Mean(s.e.m.) best DO_2I (ml min^{-1} m^{-2})	639(9·4)	447·3(19·6)
Mean change in heart rate (beats per min)	88 up to 91	88 up to 92
Median (range) preop. intravenous fluid (ml)	1025 (0–6825)	1150 (100–4600)
Median (range) 24-h periop. fluid (ml)	5600 (2750–10 700)	4175 (2200–17 700)
Median (range) ITU stay (h)	48 (24–600)	48 (12–1224)
Median (range) hospital stay (days)	27 (3–97)	18 (2–96)
Observed complications* (%)	9 (64)	17 (65)
Predicted complication rate (%)	93	89
Observed death before 28 days* (%)	3 (21)	9 (35)
Predicted mortality rate (%)	59	55

*Values in parentheses are percentages. ASA, American Society of Anesthesiologists; POSSUM, Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity; OSS, Operative Severity Score

65 per cent for those who acheived or failed to achieve the target DO_2I respectively, and was lower, although not significantly so, than the POSSUM-predicted morbidity rate of 93 and 89 per cent respectively.

The mortality rate for both groups was lower than the POSSUM-predicted mortality rate. Although the mortality rate was more than halved in one group and nearly halved in the other from that predicted, this improvement was not statistically significant.

Discussion

A policy of perioperative enhancement of oxygen delivery was introduced in 1992 for surgical patients at high risk of significant postoperative morbidity and mortality. This uncommon but aggressive perioperative multidisciplinary policy was introduced following a study carried out at this hospital which had shown a 75 per cent reduction in mortality rate and a halving of the mean number of complications per patient[1].

As a result of an excess of emergency admissions over available ITU beds during the winter of 1994–1995 it was impossible to adhere to the previous policy of admitting to the ITU before operation all patients who fulfilled the criteria for perioperative enhancement of oxygen delivery. Consequently it was possible to conduct a retrospective audit to compare outcome for patients on the general surgical ward *versus* two types of ITU care. This study examined whether this forced rationing affected outcome while still allocating the greater proportion of resources to the most ill.

Shoemaker *et al.*[7] in 1988 showed that patients requiring major surgery and who also had pre-existing physiological impairment of one or more major organ systems were at major risk of perioperative complications and death. They also suggested that if this group of patients had cardiovascular and respiratory physiology deliberately enhanced above the median values of known survivors to achieve tissue oxygen delivery of 600 ml min^{-1} m^{-2}, then complication and mortality rates could be reduced. This work was subsequently confirmed in patients with hip fractures[16], peripheral vascular surgery[6], severe trauma[4], and general and vascular surgery[1]. More recently, however, a number of studies has suggested that this aggressive form of intervention is of dubious value[17–20]. The common feature of these later studies is that enhancement of cardiovascular physiology was applied after the patient had developed complications and was already showing signs of early organ failure. Bone *et al.*[20] studied patients only after they had already developed respiratory failure and adult respiratory distress syndrome. Hayes *et al.*[18] studied patients who were critically ill in the ITU. Many of their patients were medical patients who had not had any form of surgery. Gattinoni *et al.*[17] studied patients who had already failed to respond to conventional ITU therapy for at least 24 h before entry to the study. It would appear that this technique is of greatest benefit if instituted before surgery and maintained throughout the procedure and into the immediate postoperative period.

This audit sought to determine whether the therapy could be selectively and appropriately applied to a high-risk group of patients at a time when resources were limited. Could junior resident surgical, ITU and anaesthesia staff selectively ration resources? Results show that patients who fulfilled the criteria for entry but did not come to intensive care had a lower number of criteria and lower POSSUM and ASA scores. Using three different methods (Shoemaker criteria, ASA score or POSSUM) of assessing the patients for ITU or non-ITU treatment, the medical staff were selecting patients for preoperative or postoperative ITU care, or indeed no ITU care, very appropriately. It is impossible to ascertain retrospectively whether the selection of patients for treatment was based on scientific method (i.e. use of one of the three scores), whether they simply allocated the patients to the three different treatment groups according to their clinical impression of the severity of illness, or whether allocation depended merely on the availability of ITU beds. However, the allocation of resources seems to have been appropriate.

In answer to the second question of whether patients admitted to the ITU before operation were treated according to the protocol, only 14 of 40 patients achieved tissue oxygen delivery as high as that suggested by Shoemaker *et al.*[7]. However, despite not achieving the aims of the goal-oriented therapy, outcome was improved when these patients were compared with a previously documented database of similar patients treated in other hospitals.

Outcome was better than would have been predicted from the POSSUM score in patients who were admitted to the ITU before operation and subjected to physiological enhancement of cardiovascular and respiratory systems. It could reasonably be argued that this improvement was merely the product of the increased experienced, expertise and resources available to patients being treated in a teaching hospital. However, if this were the case, an improvement would have been expected in all patient treatment groups; this did not occur. The POSSUM database represents the outcome after surgery at a number of other hospitals in the UK, both teaching and district general hospitals. It seems that patients who went to the ITU before operation gained some advantage compared with a large reference series from a range of general and teaching hospitals.

Despite the improved outcome in patients admitted to the ITU before operation, treatment protocol goals were not achieved in 65 per cent of those sent to the ITU before operation. This may explain why the results obtained were not as good as those seen in the original controlled clinical study[1]. It was clear from the patient notes that one of the major reasons for not achieving the target of tissue oxygen delivery was impatience amongst medical and theatre staff, particularly surgical staff, to proceed to operation. This reaction is understandable, but the purpose of audit is to identify areas of practice where outcome may be improved. This audit suggests that ITU staff should be more vigorous in defence of their position in not letting patients go to theatre before they are properly prepared. However, this shift must not encourage delay in taking patients to theatre where further delay would be life threatening. Such decisions represent a difficult balance and should be taken in consultation with senior ITU, anaesthetic and surgical staff.

It would seem from this study that the preoperative physiological state of the patient is the most important factor determining outcome following major surgery. The three recorded indices of reduced physiological reserve – ASA status, POSSUM and number of Shoemaker criteria – were significantly different between the three groups of patients but OSS was almost the same. The less ill patients were being subjected to the same sort of operative intervention but their morbidity and mortality rates were considerably lower. Furthermore, although the OSS for groups of patients admitted to the ITU either before or after operation was similar, the POSSUM and ASA score were both higher in the group admitted to the ITU before operation; despite this, patients admitted to the ITU before operation had fewer postoperative complications.

Artificially dividing the three groups into 'high' and 'low' risk groups has possibly identified patients who may benefit most from this sort of multidisciplinary aggressive approach to surgery. The biggest improvement in both mortality and complication rates was in patients with the highest prediction of postoperative problems and who were admitted to the ITU before operation. The report of the National Confidential Enquiry into Perioperative Deaths[21] suggested that a common cause of postoperative death was overvigorous use of intravenous fluids causing heart failure and death. This audit does not support this view. It can be seen that some patients received as much as 22 litres of intravenous fluids over the 24 h surrounding the operation. Despite this, no patient developed heart failure due to fluid overload during the perioperative period. The authors consider that this may be due to careful monitoring of the cardiovascular status of patients and enthusiasm for the use of pulmonary artery catheters to achieve this.

This study has shown that it is possible to select patients who most require ITU care. It is clear that not all patients who fulfil the Shoemaker–Boyd criteria need intensive care before operation. Following this audit, the authors have changed the criteria for patients who require preoperative ITU 'optimization'. They now suggest that the criterion for preoperative admission and perioperative enhancement should be 'a patient whose operation is planned to exceed 90 min and who has two or more of the criteria shown in *Table 1*'.

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Soave's procedure: the final sphincter-saving solution for iatrogenic rectal lesions

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Background Restoring intestinal continuity in the presence of radiation-induced rectal lesions and following low colorectal anastomotic complications or low Hartmann's procedure may be fraught with difficulties. Soave's procedure avoids potentially hazardous perirectal dissection. This study examined the morbidity and mortality as well as functional results.

Methods Between January 1978 and July 1994 30 consecutive patients underwent Soave's operation as a final attempt to restore coloanal continuity. The pathology was radiation-induced lesions in 15 patients, low colorectal anastomotic complications in nine and low Hartmann's reconstruction in six.

Results Mean length of follow-up was 4·2 (range 1–16) years. There was no operative mortality. Early complications included one patient with postoperative haemorrhage, one with small bowel obstruction and four with pelvic or perineal sepsis. Late complications included four incisional hernias, three anastomotic strictures which were treated by dilatation, and one recurrent ischaemic colitis. Continence was normal in 19 of 23 evaluable patients.

Conclusion Soave's procedure obviates the need for extensive pelvic dissection, providing good technical and functional results in both the long and short term.

In certain rectal conditions such as radiation-induced lesions, stenosis with or without fistula following the disruption of a low colorectal anastomosis and reversal of a low Hartmann's procedure, there may be retraction of the pelvic tissues and abundant pelvic fibrosis. Rectal dissection under these conditions may be hazardous and even dangerous; risks include haemorrhage and injury to the pelvic nerves and neighbouring organs such as the vagina, ureters and iliac vessels. Under these circumstances, Soave's operation, which consists of a transrectal coloanal sleeve anastomosis without the need for perirectal dissection, may provide the final opportunity to restore continuity, the alternative being definitive colostomy.

Soave's operation was originally described in 1964 for the treatment of Hirschsprung's disease[1] and is still used by a few authors for this indication[2,3]. In 1972, Parks described a similar operation for the treatment of benign rectal conditions in adults[4], and some surgeons advocate this operation in severely constipated young patients to avoid pelvic nerve injury[5,6].

This study examined the technical and functional results of Soave's operation for patients with iatrogenically induced rectal lesions in whom colostomy was being considered or had already been constructed.

Patients and methods

Thirty consecutive patients underwent Soave's operation between January 1978 and July 1994 for the following rectal conditions: radiation-induced lesions ($n = 15$), low colorectal anastomotic complications ($n = 9$) and low Hartmann's reconstruction ($n = 6$). Case records for all patients were reviewed retrospectively. In addition 25 patients were interviewed in late 1995.

There were ten men and 20 women of mean age 54 (range 23–82) years. Twenty-eight patients had had one or more previous rectal resections and 15 had had a previous colectomy. Twenty-one patients had a history of pelvic sepsis, of whom 18 had a rectal fistula at the time of surgery, and 24 already had a colostomy. Twenty-eight patients had severe pelvic fibrosis. The mean time interval from complication to Soave's procedure was 19 (range 1–79) months. Where the initial diagnosis had been malignancy, the procedure was performed only after examination and investigations had proved there was no pelvic recurrence. All patients had a digital rectal examination and a contrast enema to provide information about rectal stump length and distensibility, and to demonstrate the presence of a stricture or fistula.

Operative technique

Surgery was performed in the Lloyd-Davies position. The left colon was completely mobilized after division of the inferior mesenteric artery at its origin and division of the inferior mesenteric vein at the inferior border of the pancreas. This latter manoeuvre is important to allow complete mobilization of the left colon into the pelvis. The left colon was then transected using a stapler at a suitable healthy and well vascularized site. To ensure that there was sufficient colon to reach the anal verge, the length of the remaining colon was shown to extend at least 3 cm below the pubic symphysis. In five patients the left colon was absent, too short or devascularized due to insufficiency of Riolan's arcade. In these patients the transverse colon was brought down transmesenterically (two cases) or the inverted right colon was used (three). Suprarectal dissection was necessary to clear adherent small bowel or omentum.

The rectal stump was identified either by following the colon down to the complicated colorectal anastomosis or by using Hegar bougies passed transanally in the patients with a short Hartmann's stump. At that level, the rectal stump was often fibrotic and stuck to the sacrum or vagina. Rectovaginal fistulas were ignored and left *in situ*. In the presence of a rectovesical fistula, the bladder was either sutured externally or repaired from within the lumen. To preserve neighbouring pelvic structures, perirectal dissection was not attempted. The rectal stump was incised transversely over a bougie and rectal mucosectomy was started and conducted downwards as low as possible after submucosal infiltration with 1:50 000 saline–adrenaline solution.

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The mucosectomy was then completed via a perineal approach from the dentate line upwards. The mucosal sleeve length was recorded in 24 operation notes, the mean length being 6·2 (range 3–12) cm. The rectal muscular sleeve left in place had to allow the passage of three fingers. If this was not possible, a vertical incision was made through the posterior rectal wall and long scissors were forced open in the upper rectum to stretch the pelvic fibrosis. Once the space within the rectal muscular sleeve was considered large enough, the stapled colon was delivered through this sleeve to the anus using triangular forceps. The opening of any previously ignored rectovaginal fistula was thereby obliterated by the new colon and allowed to heal spontaneously.

Four 4–0 reabsorbable sutures were placed at 12, 3, 6 and 9 o'clock to fix the colon in place and to avoid any tension on the anastomosis. The colon was transected at the level of the dentate line and a handsewn straight coloanal anastomosis was performed using 4–0 reabsorbable sutures and protected by a temporary loop ileostomy. The anastomosis was drained transanally for 48 h and two pelvic suction drains left in place for 3–6 days after surgery. The ileostomy was closed 6–8 weeks later, once clinical and radiological assessment of the anastomosis had been made. Patients were reviewed systematically at 1, 3, 6 and 12 months and then annually.

Results

Mortality and early morbidity

There was no perioperative mortality. Early surgical complications occurred in eight patients. One patient had postoperative pelvic bleeding requiring relaparotomy for haemostasis. One patient had a small bowel volvulus also requiring relaparotomy. Another developed a pelvic abscess which was drained transanastomotically under general anaesthesia.

Of the 18 patients who presented with fistulas, two developed recurrent rectovesical fistulas; one was successfully managed conservatively by transanal irrigation and a strict low-residue diet and the other required colectomy and repeat anastomosis. A third patient developed a recurrent rectovaginal fistula, which healed after reconstruction of a defunctioning colostomy.

One patient had a wound abscess after ileostomy closure. No patient complained of urinary retention or sexual difficulties. Medical complications included pulmonary embolism in one patient and urinary tract infection in three.

Long-term outcome

Two patients were lost to follow-up, at 2 months and 3 years. Three patients died from intercurrent disease at 3, 4 and 5 years, and one patient died from local recurrence and liver metastases at 3 years. Seven of the 28 patients who were followed developed eight late complications. Four patients developed incisional hernias, three at the ileostomy site and one along the laparotomy wound. Anastomotic strictures occurred in three patients who were all successfully treated by dilatation. One patient, who had had a Hartmann procedure for acute ischaemic colitis, developed ischaemic lesions within the transplanted colon 3 years after the Soave operation. This was treated conservatively and the patient did not require further surgery. Two patients who initially had cancer developed a second adenocarcinoma within the remaining colon, at 7 and 8 years.

Table 1 Symptoms at the end of follow-up in 23 patients

Symptom	No. of patients
Continence	
Normal	19
Incontinence to flatus	3
Incontinence to stools	1
Bowel frequency per day	
1–3	18
4–6	4
7–9	1
Good discrimination between stool and flatus	23
Urgency	5
Fragmentation of stool	5
Abdominal pain	2
Perineal pain or straining	2
Enema use	5
Diet	8
Subjective appreciation	
Very well	13
Well	7
Poor	2
Very poor	1

Functional clinical results

Mean follow-up was 4·2 (range 1–16) years. Two patients of the 25 interviewed were still waiting for ileostomy closure; therefore function results were available for 23 patients (*Table 1*). In all but three patients, a clear improvement was demonstrable during the first postoperative year. At the end of follow-up, continence was abnormal in four patients. Poor results for continence did not appear to be related to age or pathology: the mean age of the four incontinent patients was 44 (range 37–59) years and initial pathology was a radiation-induced lesion in two, a colorectal complication in one and Hartmann's reconstruction in one.

Discussion

Rectal conditions such as severe irradiation injury to the rectum and pelvis[8–14], low colorectal anastomotic fistula or stenosis[15–17] and low Hartmann procedures[16] share the same features of the presence of an inflamed and fibrosed pelvis that renders perirectal dissection difficult and hazardous. Frequently, permanent colostomy is thought to be the only alternative in such conditions, as it was in the first 24 of the 30 patients in this series. Coloanal sleeve anastomosis has been advocated to manage these difficult conditions and preserve sphincter function.

Other conditions that render complete rectal wall excision hazardous because of the risk of haemorrhage include diffuse cavernous haemangioma of the rectum[18–20] and colitis cystica profunda[21]. In these cases Soave's procedure is a safe alternative to abdominoperineal excision of the rectum.

Mortality and morbidity in this series compare favourably with that in other series (*Table 2*). Fistulas recurred in three of 18 patients who had this complication at the time of Soave's procedure. Conservative treatment in one of these patients and reoperation in the other two led to complete healing in all cases. No patient complained of sexual urinary dysfunction, and this relatively low complication rate may be attributed to the operative technique itself, which avoids all deep pelvic dissection.

Long-term functional results in this series appear to be satisfactory, with 19 of 23 patients achieving normal conti-

Table 2 Complications and mortality in patients undergoing coloanal sleeve anastomosis

	Present series ($n = 30$)	Gazet[9] ($n = 13$)	Nowacki *et al.*[11] ($n = 15$)	Browning *et al.*[12] ($n = 10$)
Mortality	0	1	1	0
Septic complication	4	1	3	4
Recurrent fistula	3	1	3	NA
Haemorrhage	1	NA	NA	1
Bowel obstruction	1	1	NA	NA
Anastomotic stricture	3	5	2	6

NA, information not available

nence. However, there remain a few patients who have continuing urgency, fragmentation of stools and a high frequency of defaecation. One explanation for this could be the decreased colonic distensibility in the fibrosed pelvis[22] due to irradiation, colorectal anastomotic complications or multiple previous operations. Cooke and Wellsted[10] reported the results of coloanal sleeve anastomosis in 59 patients operated on for radiation-induced rectal damage. The perioperative morbidity rate in this series was 24 per cent and there were four technical failures resulting in permanent colostomy. Of the 46 patients who had been followed for more than 1 year after closure of the colostomy, 35 were continent, seven had control of solid faeces but not of flatus or liquid stools, and four were completely incontinent. In contrast, only one patient in the present series was incontinent to stools. Similar results have been reported by other groups with satisfactory continence rates of 76 and 87 per cent following coloanal sleeve anastomosis performed for a variety of rectal conditions[2-9].

In conclusion, benign rectal conditions such as radiation-induced damage to the rectum, low colorectal anastomotic fistulas or stenosis, and reconstruction after low Hartmann procedures, may all be associated with difficult and potentially dangerous pelvic dissection. Soave's procedure obviates the need for extensive dissection of the lower rectum and offers good technical and functional success in both the short and long term.

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Lack of telomerase in desmoids occurring sporadically and in association with familial adenomatous polyposis

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Background Telomerase activity may be required for unlimited growth of cells and is repressed in most somatic tissues, but is detectable in immortal cell lines, germ cells, many malignancies and some benign lesions. Desmoids are proliferative, locally invasive, non-metastasizing fibromatous tumours which rarely regress. They occur frequently in familial adenomatous polyposis (FAP), causing significant morbidity and death. Telomerase activity was assayed in desmoids from patients with and without FAP to assess the role of telomerase in the development of these lesions, and its potential as a prognostic marker and possible target for treatment.

Methods Protein extracts from 11 desmoids from nine patients with FAP, and ten desmoids from ten patients without FAP, were analysed for telomerase activity by the telomeric repeat amplification protocol, a sensitive polymerase chain reaction-based assay. Six fibrosarcomas and a fibrosarcoma cell line were used as positive controls; all displayed telomerase activity.

Results No telomerase activity was detected in any of the 21 desmoids studied.

Conclusion These results indicate that desmoid tumours are one of the intriguing exceptions to the emerging view that re-expression of telomerase activity accompanies the development of preneoplastic and neoplastic tissues, and suggest that alternative mechanisms may operate in these proliferative neoplasms.

Human telomeres are regions found at the ends of each chromosome which consist of the nucleotide sequence TTAGGG repeated up to 1000-fold. They appear to have two functions: the first is to protect chromosomes from recombination and loss; the second is to resolve the 'end-replication problem' which predicts the progressive and potentially catastrophic shortening of the 3′ end of DNA molecules over many cycles of replication, a problem imposed by the fact that DNA polymerization is initiated from the site of a bound RNA primer and can proceed only in the 5′ to 3′ direction. This problem is overcome by telomerase, a ribonucleoprotein that synthesizes TTAGGG telomeric repeat sequences and fuses them to the 3′ terminus of the chromosome[1–3].

It has been suggested that shortening of telomeres with cell division in the absence of telomerase activity may provide a mechanism to limit the proliferative capacity of normal cells, which senesce and stop dividing after undergoing a given number of cell divisions[3–5]; conversely, activation of telomerase may be required to allow cells to escape from senescence and to proliferate indefinitely. This is supported by the finding that there is no telomerase activity in most human somatic cells, whose telomeres shorten with replicative age[6], and that telomerase activity is present in germ cells and many malignant tumours and immortal cell lines[3,7–12].

Desmoid tumours are rare, but are an important extracolonic manifestation of familial adenomatous polyposis (FAP). They have been reported to occur in about 10 per cent of patients with FAP[13–15] and are one of the two commonest causes of death in patients who have had prophylactic colectomy for this condition[16,17]. They may occur at any site, but show a propensity for the small bowel mesentery, retroperitoneum and abdominal wall in FAP[18].

The pathogenesis of desmoid tumours is not clearly understood. They are classified as fibromatoses[19], which result from infiltrative proliferation of well differentiated fibroblasts, and show repeated local recurrence but no features of unequivocal malignancy or inflammation. Desmoid tumours are locally invasive, but do not metastasize. The only convincing report of malignant transformation (to fibrosarcoma) occurred in a desmoid treated with radiotherapy[20]. There is evidence that desmoids are clonal in composition[21] and carry a 'second hit' mutation in the *APC* gene, and therefore are true neoplasms[22–25].

The levels of telomerase activity have been assayed in specimens of desmoid tumours from patients with and without FAP to assess the role of telomerase in the development of these lesions, and its potential as a prognostic marker and possible target for treatment.

Patients and methods

Patients

A total of 11 desmoid tumours from nine patients with FAP, ten desmoid tumours from ten patients without FAP and six fibrosarcomas were analysed for telomerase activity. Details of the patients from whom specimens were taken are given in *Table 1*. All of these tumours were sufficiently large and symptomatic to require surgical treatment.

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Table 1 Details of patients

Patient no.	Sex	FAP	Age at surgery (years)	Tumour type	Tumour site
1	F	Yes	25	Desmoid	Intra-abdominal
2	M	Yes	27	Desmoid	Intra-abdominal
			30	Desmoid	Intra-abdominal
3	F	Yes	40	Desmoid	Abdominal wall
4	F	Yes	30	Desmoid	Abdominal wall
5	M	Yes	38	Desmoid	Intra-abdominal
			39	Desmoid	Intra-abdominal
6	F	Yes	28	Desmoid	Abdominal wall
7	F	Yes	20	Desmoid	Abdominal wall
8	M	Yes	36	Desmoid	Abdominal wall
9	M	Yes	36	Desmoid	Intra-abdominal
10	M	No	16	Desmoid	Popliteal fossa
11	F	No	36	Desmoid	Abdominal wall
12	M	No	34	Desmoid	Axilla
13	F	No	n.a.	Desmoid	Shoulder
14	M	No	44	Desmoid	n.a.
15	F	No	n.a.	Desmoid	Calf
16	M	No	n.a.	Desmoid	n.a.
17	F	No	15	Desmoid	Thigh
18	M	No	41	Desmoid	n.a.
19	F	No	n.a.	Desmoid	Pubis
20	M	No	25	Fibrosarcoma	Thigh
21	M	No	n.a.	Fibrosarcoma	n.a.
22	F	No	n.a.	Fibrosarcoma	n.a.
23	M	No	43	Fibrosarcoma	n.a.
24	F	No	50	Fibrosarcoma	n.a.
25	M	No	61	Fibrosarcoma	Thigh

FAP, familial adenomatous polyposis; n.a., Data not available

Preparation of lysates

After excision the samples were snap frozen in liquid nitrogen and stored at −80°C. Each specimen (50–100 mg) was homogenized in 200 µl 3-[(3-chloramidopropyl)dimethylamino]-1-propanesulphonate lysis buffer (Sigma, Poole, UK). After 25 min on ice the lysate was centrifuged at 16 000 *g* for 20 min at 4°C. The supernatant was quickly frozen on dry ice and stored at −70°C. The protein concentration of the extract was measured using a micro protein determination kit 610-A (Sigma). Extracts of the fibrosarcoma cell line HT1080 were prepared by washing cells in phosphate buffered saline, collecting by centrifugation, resuspending in ice cold wash buffer (HEPES–potassium hydroxide (pH 7·5) 10 mmol/l, magnesium chloride 1·5 mmol/l, potassium chloride 10 mmol/l, dithiothreitol 1 mmol/l), collecting again by centrifugation and then resuspending in 20 µl ice cold lysis buffer per 10^6 cells. After 30 min on ice the lysate was centrifuged at 100 000 *g* at 4°C. The supernatant was processed in the same way as the tissue extracts.

Assay for telomerase activity

Telomerase activity was assayed by the telomeric repeat amplification protocol (TRAP)[8]. Positive controls for the TRAP assay consisted of the six fibrosarcomas and a fibrosarcoma cell line (HT1080) known to contain active telomerase. Aliquots of extracts containing 6 µg protein were incubated for 10 min at room temperature in Tris–hydrochloride (pH 8) 20 mmol/l, magnesium chloride 1·5 mmol/l, potassium chloride 63 mmol/l, 0·005 per cent Tween, ethylene glycol-bis(b-aminoethyl ether)-N,N,N′,N′-tetra-acetic acid 1 mmol/l, 1 µg T4g32 protein (Pharmacia, St Albans, UK), 2′-deoxyribonucleoside 5′-triphosphates 50 mmol/l, 4 µg bovine serum albumin, 0·1 µg TS oligonucleotide (5′AATCCGTCGAGCAGAGTT-3′) and 3 µCi [^{32}P]2′-deoxycytidine 5′-triphosphate (3000 Ci/mmol) to allow for extension of oligonucleotide TS by telomerase. Some 0·1 µg CX primer (5′-CCCTTACCCTTACCCTTACCCTAA-3′) and 2 units Taq polymerase were then added and the reaction mixture was subjected to 27 polymerase chain reaction cycles at 94°C for 30 s, 50°C for 30 s and 72°C for 90 s. Half of the product (25 µl) of each reaction was analysed by electrophoresis in 0·5 × Tris-borate ethylenediamine tetra-acetic acid on 10 per cent polyacrylamide non-denaturing gel. Gels were dried and autoradiographed at −70°C with intensifying screens for up to 40 h. Telomerase activity was detected as a six-nucleotide repeat ladder. Extracts were considered negative if no telomerase products were detected after a 40-h exposure.

The experiments were repeated, incubating 5 µl of all cell extracts with 1 µg RNase A (Sigma) for 15 min at 37°C, before subjecting them to the TRAP assay. Desmoid samples were re-assayed using a volume of cell extract equivalent to 60 µg and 0·6 µg protein, and extracts from the positive control cell line HT1080 were subjected to the TRAP assay after the addition of desmoid cell extract equivalent to 6 µg protein.

Results

Telomerase activity was not detected in any of the desmoid samples under standard TRAP assay conditions using a volume of cell extract containing 6 µg protein (*Fig. 1*). However, all six of the fibrosarcoma samples were found to express telomerase activity. This was shown to be sensitive to ribonuclease (RNase) since incubation of cell extract with RNase A resulted in elimination of this activity, as it did in the fibrosarcoma cell line HT1080 extract (*Fig. 2*).

The inability to detect telomerase activity in desmoid extracts may be a true indicator of the absence of telomerase activity or could result from the presence of inhibitory factors, as reported by others[7,10]. When desmoid samples were re-assayed using a tenfold increase in concentration of extract in order to allow detection of weak telomerase activity, or ten-fold dilutions, on the assumption that putative inhibitors would be diluted away, telomerase activity was not detected (data not shown). Addition of desmoid extracts to extracts from the positive control cell line, to determine whether the desmoid

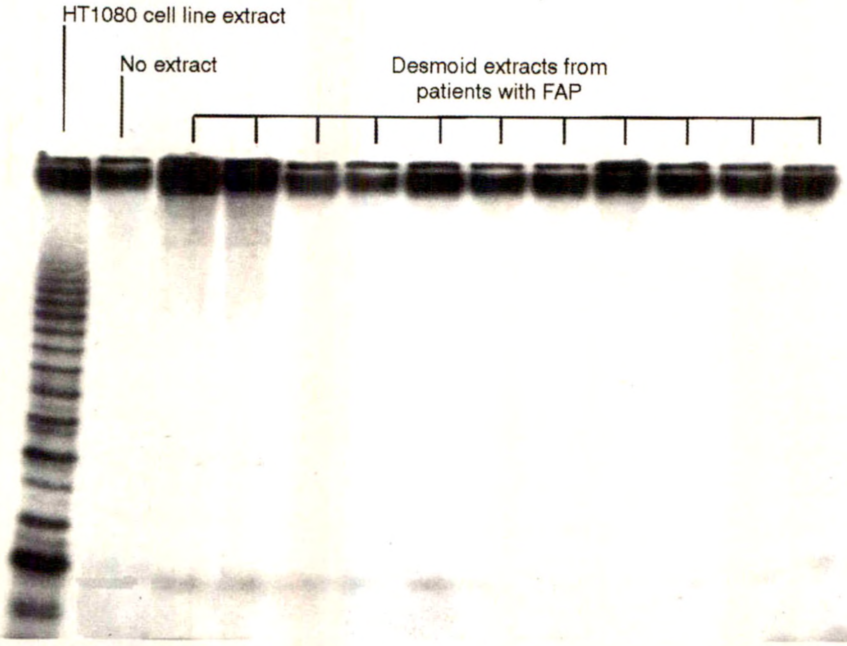

Fig. 1 Lack of telomerase activity in cell extracts from desmoid samples from patients with familial adenomatous polyposis (FAP). An extract from the fibrosarcoma cell line HT1080 served as a positive control, producing the characteristic six-basepair ladder. The negative control contained no extract

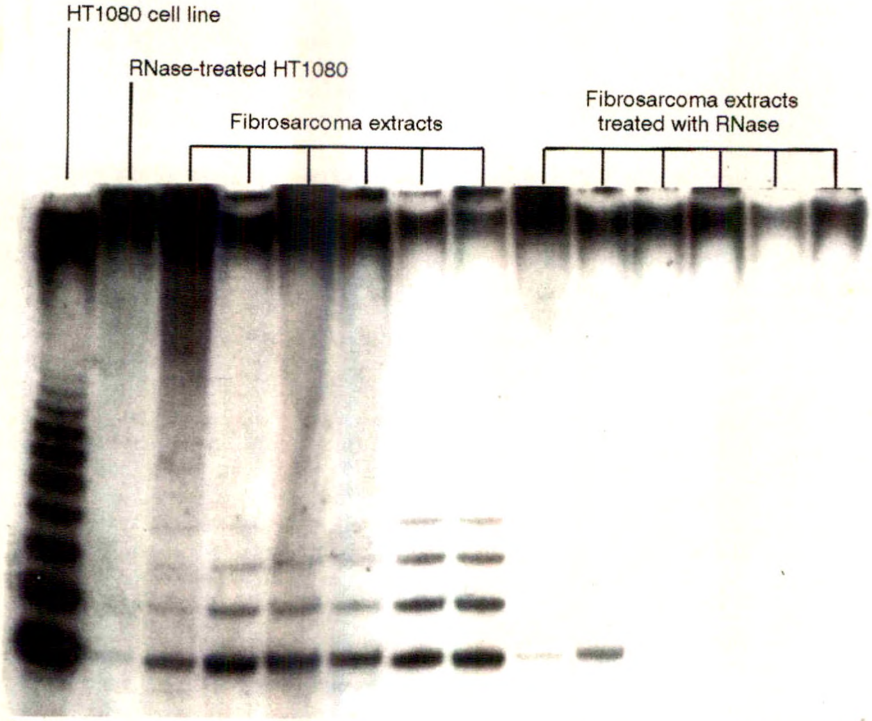

Fig. 2 Telomerase activity in extracts from fibrosarcoma samples. Treatment with RNase before analysis in the telomeric repeat amplification protocol resulted in elimination of the six-basepair ladder in all of the fibrosarcoma extracts and in the HT1080 extract

extracts could inhibit telomerase activity of the positive control, did result in a reduction of the telomerase signal in four of the 11 desmoid samples from patients with FAP and two of the ten desmoid samples from those without FAP (*Fig. 3*). This suggests that some of the desmoid extracts did indeed contain inhibitory factors, either to telomerase activity or to the TRAP assay. However, these inhibitory factors were not strong enough completely to

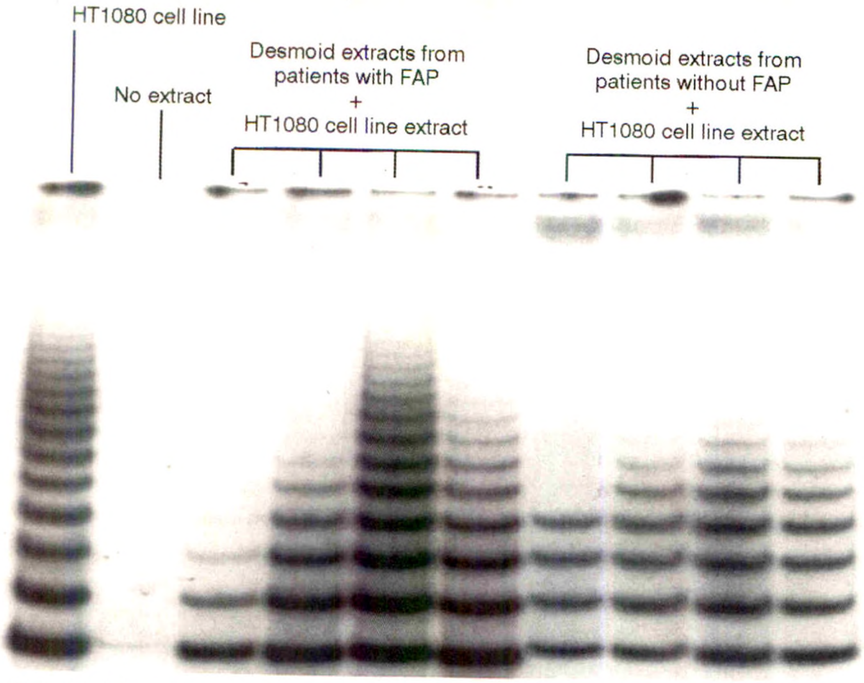
HT1080 cell line
No extract
Desmoid extracts from patients with FAP + HT1080 cell line extract
Desmoid extracts from patients without FAP + HT1080 cell line extract

Fig. 3 Examples of the effect of adding cell extracts from desmoid samples to extracts of the positive control. FAP, familial adenomatous polyposis

inhibit the telomerase signal. It is unlikely, therefore, that any of the desmoid extracts gave false-negative results for telomerase activity.

Discussion

These results demonstrate that telomerase activity was not present in the desmoids investigated, whether they originated in patients with or without FAP, and that the inability to detect telomerase activity could not be accounted for by inhibition of the assay by cell extracts. Moreover, although desmoids show varied cellularity, it is unlikely that this result could have been caused by a lack of cells in the tissues studied as the TRAP assay is highly sensitive, detecting telomerase activity in as few as 100 positive cells or as few as 0·001 per cent positive cells in a mixed population[8]. That telomerase activity can be re-expressed in malignant tissue of fibroblastic origin was demonstrated by the fact that all of the six fibrosarcomas gave strongly positive results in the TRAP assay.

Although desmoids do not display unequivocal features of malignancy and do not metastasize, they can exhibit aggressive local invasion and recurrence and can grow to a very large size. Desmoids from patients with FAP display certain features of neoplasia, the most notable being the loss of both normal alleles of the *APC* gene, one copy being lost by germline mutation and the second by somatic mutation or by microdeletion[25,26], in common with colorectal adenomas and cancers in FAP. It appears, therefore, that somatic mutation of the *APC* gene is an early and crucial event in the formation both of adenomas and desmoids, since mutations in other genes known to be involved in the development of colorectal cancer, such as K-*ras* and *TP53*[27], are very rare or absent in adenomas and desmoids[25,28].

Studies of other neoplastic but non-malignant tissues indicate that re-expression of telomerase activity is by no means unknown. For example, Tahara *et al.*[7], using specimens from patients without FAP, detected telomerase activity in colorectal and gastric adenomas and gastric intestinal metaplasia, and concluded that reactivation of telomerase may occur at an early stage of carcinogenesis. However, in another study[29] there was no detectable telomerase activity in colorectal or duodenal polyps from patients with FAP or in colonic polyps from patients with colon cancer but not FAP. These authors concluded that detectable telomerase activity correlates with acquisition of malignancy from benign adenomatous polyps to invasive colorectal cancer. Hepatitic and cirrhotic liver[30], skin papillomas[31], and dysplastic and hyperplastic head and neck lesions[32] are other potentially premalignant tissues found to express some telomerase activity. Low levels of activity have also been reported in breast fibroadenomas[9]. Sun-damaged skin expresses higher telomerase activity than does normal skin, but lower activity than is found in basal cell carcinomas, squamous cell carcinomas and melanomas[33]; in neuroblastomas, telomerase is generally expressed at low levels in tumours with a favourable prognosis and at very high levels in tumours with an unfavourable prognosis[11]. Thus there is evidence for the lifting of telomerase repression in some regenerative lesions and benign tumours as well as frank malignancy. Conversely, a significant proportion of retinoblastomas (50 per cent)[34] and glioblastomas (25 per cent)[35] have been shown to develop in the absence of telomerase activity. This may be possible because they arise at a young age when telomeres are still relatively long, or they may follow an alternative pathway of telomere maintenance.

The extent to which the 21 desmoids examined in this study are typical of desmoids in general, in that they do not express telomerase activity, requires further study. However, the present results suggest that desmoid tumours are one of the intriguing exceptions to the emerging pattern that re-expression of telomerase activity accompanies the formation of regenerative, preneoplastic and neoplastic tissues. The lack of telomerase activity in desmoids suggests that mechanisms, currently unknown, other than reactivation of telomerase activity may operate in these proliferative neoplasms.

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Identification and progression of a desmoid precursor lesion in patients with familial adenomatous polyposis

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Background Desmoid tumours occur in about 10 per cent of patients with familial adenomatous polyposis (FAP), and are an important cause of morbidity and death. The natural history of desmoids was investigated by documenting prospectively the prevalence and progression of possible precursor lesions.

Methods A group of patients with FAP and controls were examined at laparotomy. Another group, with FAP and no clinical evidence of desmoid, and a group of controls, underwent abdominopelvic computed tomography.

Results At laparotomy 13 of 42 patients with FAP had fibromatous mesenteric plaques; seven of these had not had surgery. Seven had more extensive mesenteric fibromatosis and had undergone significantly more laparotomies than the rest. Of 103 patients scanned, two had desmoid tumours and 22 (21 per cent) had mesenteric fibromatosis. On follow-up both desmoid tumours grew rapidly; mesenteric fibromatosis was unchanged in eight and resolved in four of the 12 patients rescanned.

Conclusion A model of desmoid tumour development is suggested, analogous to the adenoma–carcinoma sequence, in which a less benign phenotype emerges as molecular genetic abnormalities accumulate: mesenteric plaque-like desmoid precursor lesions arise in many patients with FAP before surgery as a result of abnormal fibroblast function; some, perhaps stimulated by surgery, progress to mesenteric fibromatosis; these in turn can give rise to desmoid tumours.

Familial adenomatous polyposis (FAP) is an autosomal dominantly inherited disorder due to germline mutation of the tumour suppressor gene *APC*, which occurs with a frequency of one in 7500[1]. Multiple large bowel polyps usually develop in adolescence or early adulthood, with inevitable progression to colorectal carcinoma if not treated; affected individuals are managed either by prophylactic restorative protocolectomy (RPC) or colectomy and ileorectal anastomosis (IRA) with surveillance of the rectal remnant.

Desmoid tumours are one of a range of extracolonic manifestations of FAP, and have been reported to occur in about 10 per cent of these patients[2]. They are poorly understood, locally invasive, non-metastasizing neoplasms[3] which occur particularly in the small bowel mesentery. Intra-abdominal desmoid tumours are an important source of morbidity in FAP, and are one of the commonest causes of death in these patients[4,5]. Treatment is difficult and based largely on anecdote; it has been suggested that medical treatment of very early desmoids might be more effective[6].

There is evidence that trauma (particularly surgical), oestrogens and genetic factors all have a role in desmoid formation[2], and somatic mutation of the *APC* gene has been documented in these tumours[7–11]. However, their precise aetiology and natural history remain obscure. Areas of diffuse mesenteric fibromatosis have been observed in patients with FAP, and it has been suggested that these might enlarge to form a desmoid tumour[12]. Such progression has been observed in a retrospective study in which computed tomography (CT) scans of patients subsequently diagnosed with desmoid tumour were reviewed[13]; mesenteric stranding or whorled mesenteric thickening (*Fig. 1*), sometimes associated with bowel tethering, was seen to progress to form a desmoid

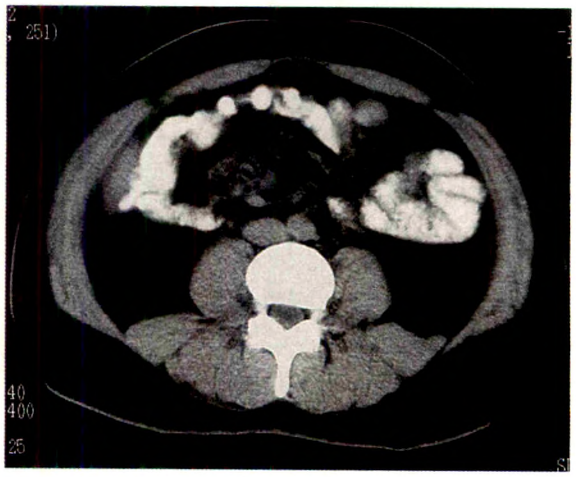

Fig. 1 Computed tomography scan showing whorled mesenteric thickening, compatible with mesenteric fibromatosis

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tumour. However, the origin of these abnormalities and the frequency with which they occur or give rise to desmoid tumours in patients with FAP is not known. This prospective study was undertaken to identify early abnormalities in the small bowel mesentery of patients with FAP and to document their subsequent progression.

Patients and methods

Intraoperative examination

A detailed examination was made of the small bowel mesentery of all patients with FAP undergoing laparotomy over a period of 18 months. In addition, a group of control patients, without FAP, undergoing laparotomy was examined in the same way. Biopsies of abnormal areas were taken for histological examination

Computed tomography screening

Patients with FAP were recruited at outpatient visits; those who were under 16 years old, pregnant, had symptoms suggestive of desmoid (abdominal pain or awareness of an abdominal mass), with an abdominal mass on clinical examination or with a diagnosis of desmoid in the past were excluded. The patients underwent helical abdominopelvic CT with oral contrast. A control group of eight volunteers underwent a limited CT examination of the abdomen, specifically to image the small bowel mesentery. These patients had been treated for chronic constipation by total colectomy and did not have FAP. All the scans were reported by two consultant radiologists specialized in cross-sectional imaging; the results were reached by consensus. Patients with evidence of desmoid tumour or mesenteric fibromatosis were invited for a single repeat CT scan after approximately 6 months. Approval for this study was obtained from the Harrow Research Ethics Committee and the East London and City Health Authority Research Ethics Committee, and written informed consent was obtained from all subjects.

Results

Intraoperative examination

Forty-two patients with FAP (median age 28 (range 13–53) years; 23 male) and 13 controls were examined at laparotomy. There was no significant difference between these groups in terms of age, sex or number of previous laparotomies. Seventeen patients with FAP had mesenteric abnormalities, consisting of plaque-like areas of peritoneal thickening (*Fig. 2*) in ten and of mesenteric fibromatosis in four; a further three patients had both types of abnormality. All but two of these lesions were biopsied and were found to be histologically compatible with desmoid. The only abnormality in the control group was a small peritoneal streak seen in one patient ($P < 0{\cdot}05$, two-tailed Fisher's exact test).

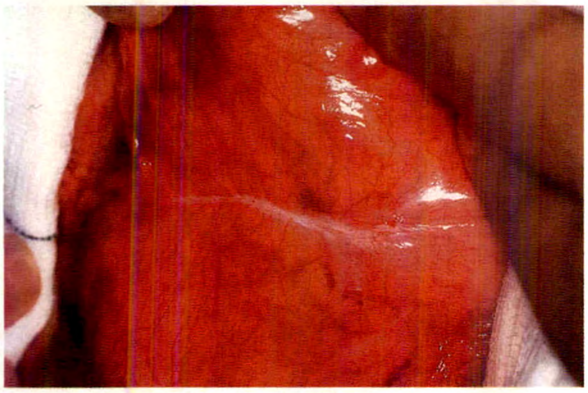

Fig. 2 Fibromatous plaque on small bowel mesentery

Seven of the ten patients with FAP with a plaque only had not had abdominal surgery, whereas all of those with mesenteric fibromatosis had a history of at least one laparotomy. Those with mesenteric fibromatosis had undergone more laparotomies (mean(s.d.) 2·0(1·0)) than those without (0·4(0·7)) ($P = 0{\cdot}001$, Mann–Whitney *U* test). There was no relationship between patients' age, sex, parity or oral contraceptive use and the findings at laparotomy; none of these patients had a family history of desmoid.

Computed tomography screening. One hundred and three patients with FAP (median age 36 (interquartile range 30–48) years; 54 (52 per cent) men) were investigated. Two were found to have a clinically unrecognized desmoid tumour and a further 22 (21 per cent) had mesenteric abnormalities consisting of stranding or whorled thickening, similar to those described by others[13], and compatible with mesenteric fibromatosis. None of the control group had any abnormality.

Both patients with a desmoid tumour were within 3 years of surgery and become symptomatic within 8 weeks of CT, before being informed of the findings. Patients with abnormalities consistent with mesenteric fibromatosis had laparotomy a median of 6 (range 1–19) years previously, significantly more recently than those with a normal CT scan (median 10 (range 1–42) years) ($P = 0{\cdot}03$, Mann–Whitney *U* test). Mesenteric abnormalities were found on CT in 27 per cent of female compared with 20 per cent of male patients, in 32 per cent of women with a history of combined oral contraceptive use compared with 13 per cent of those without, and in 33 per cent of parous women compared with 16 per cent of nullipara, although none of these differences reached statistical significance. Both the patients found to have a desmoid tumour were women, and both had children. Only four patients had a first-degree relative with desmoid; two of these were found to have mesenteric fibromatosis compared with 20 of the 99 patients with no such family history.

One hundred patients (97 per cent) had already undergone prophylactic colectomy. The three patients who had never had a laparotomy had normal CT scans. Sixteen (21 per cent) of the 75 patients who had only undergone IRA had diffuse mesenteric change, compared with three of the eight who had had RPC, and two of the six who initially had IRA and later had restorative proctectomy. Both patients with desmoid tumour had undergone IRA, one laparoscopically assisted. Patients with mesenteric fibromatosis had their first laparotomy at a slightly younger age (mean(s.d.) 21(10) years) than those without (25(11) years), and had had on average more laparotomies. None of these differences was significant.

Both of the patients with desmoid tumour and 12 of those with diffuse mesenteric change have been followed up by repeat CT scanning after a mean of 10 (range 3–20) months. Both the desmoids grew rapidly. The mesenteric fibromatosis was unchanged on follow-up in eight patients and had resolved in four.

Four patients took part in both studies. Both of the patients scanned before operation had normal findings at subsequent laparotomy. One patient who had normal findings at laparotomy had a normal CT scan 8 months later, and another patient, found to have a peritoneal plaque at laparotomy, had mesenteric fibromatosis when scanned 7 months later.

Discussion

Desmoid tumours follow a variable and unpredictable course, and can resolve spontaneously[14]. Lesions of mesenteric fibromatosis, consisting of mesenteric thickening and puckering but not amounting to a mass, have been seen at laparotomy in patients with FAP[12] and their CT appearances and progression to intra-abdominal desmoid tumours have been documented[13]. That CT changes such as these were found in none of the eight patients without FAP who had undergone IRA confirms that they are unlikely to be simply a consequence of this extensive surgery.

Fibroblasts cultured from skin biopsies of patients with FAP have been shown to exhibit reduced growth inhibition[15–17], and these patients develop uglier scars and more adhesions after laparotomy than the normal population[18]. The authors suggest that the mesenteric plaques observed are desmoid precursor lesions (DPLs), and that they form as a result of this abnormality of fibroblast function. These lesions are too small to be visualized by CT. That DPLs were found at laparotomy in 13 of 42 patients, half of whom had not had previous abdominal surgery, shows that they can arise in the absence of surgical trauma.

More extensive mesenteric fibromatosis was found in seven of 42 patients at laparotomy and in 21 per cent on CT, all in patients who had undergone abdominal surgery in the past. This, and the finding that patients with mesenteric fibromatosis at laparotomy had a significantly greater number of previous abdominal operations, suggests that surgery may promote the development of DPLs to the next stage of more extensive mesenteric fibromatosis. Of note in this context was the finding that the only patient with mesenteric plaques at laparotomy to have undergone CT subsequently was found to have developed mesenteric fibromatosis. It must not be forgotten, however, that both mesenteric fibromatosis and desmoid tumour can occur in patients who have never had abdominal surgery[19,20]. The reported lifetime incidence of desmoid tumour in patients with FAP is about 10 per cent in most series[2], implying that only some cases of mesenteric fibromatosis will go on to form a desmoid tumour. Moreover, the follow-up data suggest that some of these abnormalities have actually regressed over the course of this study.

Possible trends towards increased mesenteric fibromatosis formation in those with a strong family history, in women compared with men, and in parous women and oestrogen-containing contraceptive users, observed in these data are compatible with the same aetiological factors being at work in the formation of these lesions as have been described in desmoid tumours presenting clinically.

It has been suggested that RPC is associated with a higher rate of subsequent desmoid formation than IRA because of the greater surgical trauma, and that surgery at a younger age also carries an increased risk; as a result there is considerable controversy over the optimal surgery and its timing in these patients. Again the present data are compatible with this hypothesis but the sample size of this study was not sufficient to show any significant difference in the rate of desmoid formation between patients having IRA and RPC; in particular there appeared to be no difference in desmoid formation between those having RPC as their primary procedure and those having conversion to restorative proctectomy following an initial IRA.

The findings that patients with mesenteric fibromatosis on CT had abdominal surgery significantly more recently than those with a normal scan, and that the only two patients found to have a frank desmoid tumour at screening both developed clinically apparent desmoid within 2 months, are consistent with the observation that most desmoid tumours develop in the first 5 years after laparotomy. In patients who had prophylactic surgery several years before, mesenteric fibromatosis will have either progressed to clinically apparent desmoid, resulting in exclusion from this study, or will be stable or regressing. That mesenteric thickening was seen up to 19 years after laparotomy shows that these changes can persist long after other postoperative reaction in the abdomen has resolved.

In the light of the findings of this study, a model of desmoid tumour development is proposed in which DPLs form in a substantial proportion of patients with FAP before surgery, as a consequence of abnormal fibroblast function due to germline *APC* mutation; some of these progress to mesenteric fibromatosis, a change which may be promoted by surgical trauma. In some, but not all, cases this in turn can progress to form a desmoid tumour. Once a mass had formed, growth appears to be rapid, at least initially. Whether oestrogens and genetic factors influence the development of mesenteric fibromatosis from DPLs, or of desmoid tumour from mesenteric fibromatosis, or both, is not clear. This model is in many ways analogous to the adenoma–carcinoma sequence seen in the large bowel[21]; there is evidence of somatic mutation and allele loss at *APC* accompanying phenotypic change, but the stage at which this occurs and what other changes are involved remain to be elucidated.

Many of the cases of mesenteric fibromatosis detected will never develop into a desmoid tumour, and may never cause symptoms, although their presence may prevent restorative surgery. CT screening of asymptomatic patients with FAP to allow early treatment of desmoids has been suggested, but the variable progression of mesenteric fibromatosis to desmoid tumour and the rapid growth of established desmoid tumours suggests that CT appearances may give rise to unnecessary concern and add little to clinical follow-up. However, these patients need to be monitored for research purposes to document what progression does take place, and perhaps to study the effects of early treatment.

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Malone antegrade continence enema for faecal incontinence and constipation in adults

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Background In the Malone antegrade continence enema (ACE) technique the appendix or a 'neoappendix' created from the caecum is brought to the abdominal wall creating a small stoma. Thereby, antegrade enemas can be administered to empty the colorectum and prevent faecal incontinence or constipation in children with congenital malformations. The aim of this study was to describe the results of the ACE in adults suffering from faecal incontinence or constipation.

Methods In 16 adult patients (ten women and six men) suffering from severe faecal incontinence (ten patients) or constipation (six patients) the ACE procedure was performed; the appendix was used in 12 and a 'neoappendix' was created in four. Patient records were used for the description of surgical procedures and complications. Results were evaluated by a structured telephone interview.

Results After a follow-up of 1–39 (mean 17) months, four patients had stopped using the stoma because of abdominal pain or lack of effect. Among the other 12 patients overall satisfaction with the stoma was high or very high. In constipated patients mean time for defaecation was reduced from 170 to 45 min. Faecal incontinence was much reduced in eight patients; the impact on social activities and quality of life caused by bowel dysfunction was reduced in all 12 patients.

Conclusion The ACE technique can be used to treat selected adult patients suffering from faecal incontinence or constipation.

In 1990 Malone *et al.*[1] described the antegrade continence enema (ACE) technique, creating a continent stoma by implanting the tip of the appendix in a non-refluxing manner into the caecum and bringing the base out onto the abdominal wall. Through this small appendicostomy, antegrade enemas could be administered to empty the colorectum and prevent faecal incontinence or constipation. In several studies the ACE has been safe and effective among children suffering from faecal incontinence or chronic constipation due to spina bifida or anorectal malformation[2–5]. Later reports have indicated that reimplantation of the appendix to avoid faecal leakage is unnecessary and most authors simply bring out the tip of the appendix[2–4,6]. The operation can be performed synchronously with bladder reconstruction[2,7] and the technique has been modified by creating a 'neoappendix' from a tubularized caecal flap as an alternative in patients without an appendix[7,8].

Although many adult patients may benefit from the ACE, results of its use in adults have only been presented in a single study. Thus, Hill *et al.*[6] performed the operation in six adult women suffering from severe slow transit constipation. Results from the procedure in adult patients suffering from faecal incontinence have never been described. If useful, it may relieve symptoms in patients suffering from faecal incontinence or chronic constipation due to spinal cord lesions, spina bifida, cerebral palsy or thrombosis, lesions to the anal sphincters, slow transit constipation and systemic sclerosis. Therefore, more studies of the results of the ACE in adults are necessary.

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Patients and methods

From January 1993 to June 1996, 16 patients underwent the ACE procedure. There were ten women and six men aged 20–68 (mean 41) years. The clinical problem was faecal incontinence in ten patients and chronic constipation in six (*Table 1*).

Faecal incontinence was caused by cerebral thrombosis or palsy (two patients), spinal cord lesions (two patients with lesions at T2 and L1), lumbar myelomeningocele (one patient), and systemic sclerosis (one patient). In four patients faecal incontinence was due to complicated anal sphincter lesions caused by fistulas (two patients), traumatic anal injury from a motorcycle accident (one) and haemorrhoidectomy (one). Anal sphincter damage was evaluated by anal manometry and anal ultrasonography. In three patients the damage was too severe to allow sphincter reconstruction and in one patient sphincter reconstruction had failed.

Chronic constipation was caused by spinal cord lesions (two patients; one with a lesion at C5 and one with a lumbar lesion following five operations for disc prolapse), slow transit constipation, systemic sclerosis and obstructed defaecation (one

Table 1 Patients included in the study

	Predominant symptom	
Cause of symptoms	Faecal incontinence	Constipation
Spinal cord lesion/spina bifida	3	2
Cerebral thrombosis/palsy	2	—
Anal sphincter lesion	4	—
Systemic sclerosis	1	1
Slow transit constipation	—	1
Obstructed defaecation	—	1
Sequelae from hysterectomy	—	1
Total	10	6

patient each). One patient suffered from constipation and severe chronic abdominal pain after a radical hysterectomy and had attempted suicide 6 months previously because of these symptoms. The suicide attempt had resulted in a hemiparesis further worsening constipation and abdominal pain.

All patients had been treated with increased fibre intake and laxatives or suppositories for several years without effect.

Patients' records were used to ascertain the indications for the procedure, surgical procedure and postoperative complications. Thirteen patients available for follow-up underwent a structured telephone interview to describe symptoms before treatment and at follow-up, bowel emptying procedures and satisfaction with the result. The follow-up period was 1–39 (mean 17) months. Results for three patients, not available for follow-up and no longer using the procedure, were drawn from hospital records.

Interviews were taped and a questionnaire was filled out by the interviewer during the interview. To minimize observer bias the interviewer (K.K.) was not the one who had operated on the patients.

Surgical procedures

Standard bowel preparation and prophylactic antibiotics were given. A midline incision was used and, in 12 patients with an appendix, the tip of the appendix was delivered through a right iliac fossa incision. Then a small stoma was created from the appendix using a V-Y plasty in the skin[2] (*Fig. 1*), and the caecum was fixed to the abdominal wall. One patient had a bladder augmenting procedure during the same operation.

In four patients without an appendix a 'neoappendix' was created for the procedure from a tubularized caecal flap as described previously[6,8]. All procedures were performed by the same surgeon (S.L.).

Following both procedures a silicone catheter (6 or 8 Fr) was left *in situ* for 2 weeks. Colonic wash-outs were started after 10 days.

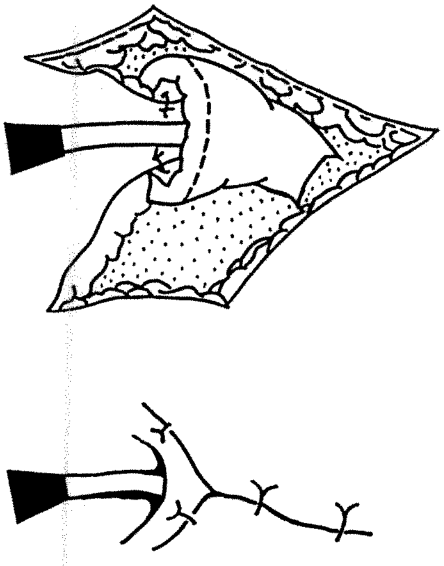

Fig. 1 Creation of a stoma from the appendix using a V-Y plasty in the skin. The V-Y plasty increases the diameter of the outer opening of the stoma and embeds it in a cutaneous fold. A silicone catheter is left in the lumen of the stoma for 2 weeks

Results

Complications

Superficial infection around the outer opening of the stoma occurred in four patients, but all were successfully treated with oral antibiotics for a few days.

Stenosis of the appendicostomy occurred in four patients. These were all treated using Hegars dilators up to three or four times. In one of these patients the stoma was revised. Stenosis of the stoma resulted in one patient discontinuing its use because of abdominal pain during wash-outs. During the operation it had been noted that the patient had a very narrow appendix possibly explaining the complication.

Faecal incontinence

Among ten patients having the ACE because of faecal incontinence six were still using the stoma at follow-up. One patient with sphincter lesions due to fistula surgery had stopped using the appendicostomy after 3 months because he was no longer incontinent even if he did not use it. One patient with disseminated mammary cancer had become too weak to perform the daily procedure. She was, however, very satisfied with the stoma because she had not suffered from faecal incontinence while using it.

Two patients had stopped using the stoma because of abdominal pain during wash-outs; in one of these this was caused by stenosis of the stoma

Among the six patients still using the stoma, five had suffered from faecal incontinence daily and one several times each week before the operation. At follow-up the frequency of incontinence episodes was much reduced in all six patients. Thus, two patients were never incontinent, three were incontinent less than once every month and one was incontinent once or more every week. Five patients used pads before the operation, but only one continued to do so at follow-up.

Constipation

Four of six patients operated on for constipation or obstructed defaecation still used the stoma at follow-up. One patient suffering from systemic sclerosis experienced no effect of the treatment. The patient who suffered from constipation and severe neurogenic abdominal pain due to a radical hysterectomy and hemiparesis had not yet tried using the stoma at follow-up because of pain around the site of incision.

Among the four patients still using the ACE, mean time for defaecation was reduced from 170 to 45 min. All felt that their problems from constipation were very much improved since the operation.

Use of the antegrade continence enema and patient satisfaction

Among the ten patients still using the stoma, four used it every day, five every second day and one every third day. Time taken to perform the enema was 15–60 (mean 30) min. All used tap water, two adding a phosphate enema to this. The volume of water used was 500–2000 (mean 967) ml. One patient with tetraplegia needed help for the procedure.

Abdominal discomfort during the enema was experienced by four patients. Five patients regularly had reflux of small amounts of water and faeces after wash-outs; however, in all five this could be controlled by an ordinary plaster. Four patients occasionally had reflux of small amounts of air from the appendicostomy. No patient felt that the appendicostomy was a major cosmetic or psychological problem.

Before the operation nine of these ten patients felt that colorectal dysfunction imposed a major restriction on their quality of life or social activities and one patient reported some restriction. At follow-up one reported that colorectal dysfunction caused some restriction while nine reported little or no restriction.

Overall satisfaction was very high in eight and high in two of the ten patients still using the procedure. Furthermore, two patients no longer using the stoma because the symptoms had disappeared or because of serious illness were very satisfied with the procedure. Thus, 12 of 16 patients operated were satisfied with the result.

Patients still using the ACE were asked to compare bowel function before the operation and at follow-up, using a scale in which 0 was the worst possible and 100 ideal. Before operation the mean score was 12 (range 0–30) while at follow-up it was 85 (range 70–100).

In the subgroup of patients with colorectal problems due to neurogenic lesions (seven patients) satisfaction with the ACE was high or very high in the six patients still using it. Among four patients with faecal incontinence due to complicated anal sphincter lesions patient satisfaction was high or very high in the three patients still using the stoma. In the mixed group of five patients with severe colorectal problems caused by systemic sclerosis, slow transit constipation, obstructed defaecation or hysterectomy the procedure was successful in three.

Discussion

This study shows that the Malone antegrade continence enema is a safe and effective treatment for selected adult patients suffering from severe faecal incontinence or constipation. Overall, the ACE was successful in 12 of 16 patients over a mean follow-up of 17 months. This is in accordance with some previous results from children suffering from faecal incontinence[2], while others have reported a higher success rate but after a shorter follow-up[3,6,7].

These preliminary results indicate that the ACE can relieve colorectal problems in patients with neurological lesions who often suffer from severe constipation or faecal incontinence[9,10]. Furthermore, the results in patients with incontinence due to severe anal sphincter lesions or neurological lesions are comparable to results from the creation of a neosphincter from the gracilis muscle[11,12] or the implantation of an artificial anal sphincter[13,14]. Therefore, the ACE technique, as a smaller operation, may be an alternative to these more extensive procedures. Furthermore, no major complications were observed and if patients find the side-effects unacceptable they can discontinue using the stoma. It will then obliterate, leaving the patient no worse than before the operation.

As in previous studies, the present results indicate that reimplanting the appendix is unnecessary. The tip of the appendix was simply brought out. The rate of success was higher among patients having an appendicostomy (ten of 12) than in patients having a 'neoappendicostomy' (two of four). Because so few patients had a 'neoappendicostomy' no explanation can be given for this difference. However, one must expect more complications, especially stenoses, in patients having a 'neoappendicostomy' since the stoma is not created from a natural luminal organ.

The most common complication was stenosis of the appendix occurring in four of 16 patients; however, this only caused one patient to discontinue use of the stoma. The frequency of stenosis is in accordance with several previous studies[2,3,6] and lower than in another[8]. The occurrence of stenoses may be reduced by instructing patients to insert a catheter through the stoma once or twice every day, even if they only use it for wash-outs every second day[2]. Also, the frequency of stenoses may be reduced by decreasing the number of superficial infections around the stoma and by ensuring that the flaps used for the creation of the V-Y plasty are well vascularized.

Most failures occurred within a few months after the operation and were caused by pain during wash-outs. The number of patients experiencing abdominal discomfort during wash-out was higher than in previous studies. This could be because a larger volume of water was used by the present patients than was used in the only other study of this procedure in adult patients[6].

The mean time required for the enema was 30 min each or every other day. This is in accordance with previous studies[1–3] and less than in another study[6]. As in previous studies[1,2,4,7], the frequency of wash-outs and the volume of water used in each individual patient was determined by trial and error during the first months after the operation. Therefore, it is most important that all patients are well motivated and understand that some time is necessary to learn the procedure. During this initial period, instructions from an experienced nurse with a special interest in this field are very important.

Since this is a minor and reversible operation, it could often be indicated in selected patients with severe constipation or faecal incontinence resistant to other therapies. However, larger studies are needed for further evaluation, and long-term results have yet to be described.

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Glutaraldehyde cross-linked collagen in the treatment of faecal incontinence

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Background The treatment of faecal incontinence secondary to internal anal sphincter dysfunction is unsatisfactory. The aim of the study was to evaluate the efficacy of anal glutaraldehyde cross-linked (GAX) collagen injections in patients with a surgically incorrectable disorder.

Methods Seventeen patients were studied: nine had idiopathic faecal incontinence, three had incontinence following haemorrhoidectomy, two following internal sphincterotomy, two following an internal sphincter defect from obstetric injury and one following treatment for fistula *in ano*. All patients were refractory to conservative treatment and were unsuitable for surgical repair. All had anorectal physiology and endoanal ultrasonography before and after GAX collagen injections.

Results All patients tolerated the injection without side-effects. All patients had an intact external anal sphincter. Following injection, 11 patients showed marked symptomatic improvement. One patient reported symptomatic improvement but remained in clinical grade 3, and two reported minimal improvement. There was no improvement in three patients, but one of these had a repeat injection and showed significant improvement subsequently.

Conclusion Injection of GAX collagen in the anal canal is a simple and well tolerated method of treating faecal incontinence due to internal sphincter dysfunction. Early results suggest it provides an easy and reliable alternative to the currently available methods that are often unsuccessful and at best unpredictable.

The aetiology of faecal incontinence is varied and includes obstetric damage to the anal sphincters, neuropathy of the sphincter muscles and the pelvic floor muscles, and iatrogenic damage to the internal and external anal sphincters during procedures such as lateral internal sphincterotomy and haemorrhoidectomy[1,2].

Repair of the external anal sphincter following obstetric and direct trauma yields good results in 70–90 per cent of patients[3,4]. Associated neuropathy yields less favourable results[4,5]. Results of surgical reconstruction of the internal anal sphincter are even less promising. Conservative treatment, although effective in some patients, is unsuccessful in the majority.

Variation in radial canal pressures has been described previously[6]. This may reflect anatomical deficiency or weakness of the sphincter muscle in a defined quadrant. Endosonographic studies of the anal canal have shown morphological asymmetry of the internal anal sphincter in patients with faecal incontinence[1].

Patients with a fissure *in ano* refractory to medical management undergo lateral internal sphincterotomy. Approximately 10 per cent of these patients develop faecal leakage or incontinence to flatus. This group often has a gutter deformity in the anal canal, which is thought to be responsible for the seepage of faecal material[7].

The use of an injectable bulk enhancing agent to increase urethral resistance at the level of the bladder neck has been tried in patients with urinary incontinence with considerable success[8]. Glutaraldehyde cross-linked (GAX) collagen, a highly purified bovine dermal collagen, has been developed for use as a periurethral bulking agent. It is biocompatable and does not begin to degrade for approximately 12 weeks after the injection. The persistence of GAX collagen has been verified histologically 9–19 months after injection[9,10]. An allergic response occurs in up to 3 per cent of patients, and subclinical seropositivity has been reported with no adverse effect[11,12].

The use of an injectable bulk-enhancing agent in the anal canal in patients with faecal incontinence has not been tested. The aim of this study was to evaluate the efficacy of anal GAX collagen injections for the treatment of idiopathic faecal incontinence in patients who have failed conservative treatment and have a surgically incorrectable problem.

Patients and methods

Seventeen patients (five men, 12 women), aged 42–76 (mean 53) years, were recruited to the study. Nine patients had idiopathic faecal incontinence secondary to weakness of the internal anal sphincter. Three patients were incontinent following haemorrhoidectomy, two following an internal sphincterotomy, two had an internal sphincter defect following obstetric injury, and one following surgical treatment for fistula *in ano*. All patients had grade 2 or 3 faecal incontinence (incontinent to flatus and liquid stool). All patients complained of faecal leakage and soiling of underwear, had failed conservative treatment and had a surgically incorrectable problem.

All patients had anorectal physiology and endoanal ultrasonography performed before GAX collagen injections. Basal and squeeze pressures were measured before and after injection using a water-filled microballoon manometry system. Rectal volume sensation at the threshold, constant volume and maximum tolerable volume was also measured.

An intradermal test injection (0·2 ml) was given to all patients before injection of GAX collagen in the anal canal. The test result was read 1 month later and the therapeutic injection given if there was no allergic response.

The injections were performed in the left lateral position using a proctoscope, preloaded GAX collagen syringe and a Gabriel haemorrhoid injection needle. The presence of a gutter deformity or asymmetry in the anal canal was sought and

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collagen was injected submucosally either until the gutter deformity was corrected or adequate symmetrical anal cushions were raised. The injection was given in one to three positions in all patients. A maximum of 2 ml collagen was injected in one session.

Clinical outcome was measured at an interview with the patient on follow-up visits at 1 and 6 months. Continence grading after injection was established in all patients along with the frequency of incontinence episodes following the injection.

Results

All patients tolerated the injection without any ill-effects. Eleven patients showed marked symptomatic improvement. None of these leaked liquid stool or reported soiling. One patient reported symptomatic improvement, but remained in clinical grade 3 although the frequency of incontinence episodes improved, and two others reported minimal improvement. Three patients reported no improvement, but one had a repeat injection and showed significant improvement. Three patients have required repeat injections. The mean follow-up is 8 (range 4–12) months.

Anorectal physiology and endoanal ultrasonography

All patients had an intact external anal sphincter on endoanal ultrasonography. Mean resting pressures were low before operation (mean(s.e.m.) 30(11) cmH_2O) and remained low after operation (45(10) cmH_2O). Although there was a trend towards an increase in resting pressures, the differences were not significant. Similarly, squeeze pressures were not significantly different before (125(20) cmH_2O) and after (130(10) cmH_2O) injection. Rectal volume sensation was also not affected significantly by GAX collagen injections.

Discussion

Anal collagen injection is a simple procedure which can be performed easily in the outpatient department and is well tolerated and free of complications. Despite its simplicity, there is a learning curve in recognizing the area where the injections should be given.

In this study the majority of patients reported significant symptomatic improvement. In some where there was little or no initial improvement, a repeat injection provided significant symptomatic benefit. This appears to be a major advantage of this technique in that repeat injections can be given to fill keyhole deformities or raise anal cushions until the continence grade improves.

Although there was some improvement in resting and squeeze pressures after injection, this did not reach statistical significance. This is not surprising, because physiological measurements do not necessarily correlate with symptoms and low resting and squeeze pressures are fully compatable with normal continence.

Faecal incontinence as a result of trauma to the internal sphincter, either during fistula surgery or controlled division of the internal sphincter during lateral internal sphincterotomy, is associated with impairment of continence in up to 10 per cent of patients. Results of surgical reconstruction in such patients are disappointing. A flap advancement technique into the anal canal to fill the gutter or keyhole deformity following lateral sphincterotomy has been described recently[7]. Although the initial results are encouraging, it has a limited place in the management of faecal incontinence for a wide range of reasons. Even in patients in whom advancement flaps may be helpful, an initial trial with collagen to fill the deformity may be worthwhile, as seen in three patients in this study. Another possible role for GAX collagen injections is in patients with a combined internal and external sphincter defect. Combination therapy with GAX collagen and repair of the external sphincter may provide better results than repair of the external sphincter alone.

The mechanism by which collagen injection works is uncertain. It seems likely that it is purely a mechanical effect of either filling a gutter deformity or raising cushions to keep the anal canal closed, thus preventing faecal leakage. Alternatively it may provide an adequate anal lining which is bulky enough to plug the anal orifice while the internal anal sphincter contracts tonically.

Initial results from this study suggest that GAX collagen injections are a simple way of treating faecal leakage and incontinence with impairment of internal anal sphincter function or internal anal sphincter defects.

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Functional results following the antegrade continence enema procedure

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Background Forty children who underwent the antegrade continence enema (ACE) procedure for faecal soiling were studied to determine factors predictive of outcome.

Methods There were four patient groups: (1) ambulant with spinal dysraphism ($n = 13$), (2) wheelchair bound with spinal dysraphism ($n = 14$), (3) ambulant with miscellaneous disorders ($n = 11$) and (4) wheelchair bound with miscellaneous disorders ($n = 2$). Effectiveness of the procedure was assessed using technical evaluation and quality-of-life improvement (QOLI) scores (0–5). Objective assessment included colonic transit time (CTT) and anorectal manometry. Median follow-up was 21 (range 5–37) months.

Results Some 28 of 40 children achieved continence. The procedure was reversed in four of 40 children. Of the other 36 children with a functioning ACE stoma, all reported improvement in quality of life (mean QOLI score 3·5). There were no significant differences in technical evaluation score, QOLI score, CTT, manometry findings or continence between ambulant groups and the wheelchair-bound group with miscellaneous disorders. QOLI score, anorectal squeeze pressure and continence were significantly poorer in those who were wheelchair bound with spinal dysraphism. Absent squeeze pressure was associated with poor outcome.

Conclusion Wheelchair-bound children with spinal neuropathy have a poorer outcome following the ACE procedure. Although ACE is an effective method of promoting faecal continence, it is essential to determine the aetiology of incontinence and sphincter function before operation.

Faecal incontinence is a physically, emotionally and psychologically disabling symptom, predisposed by a variety of congenital and acquired disorders in childhood. These disorders notably include spina bifida, allied spinal neuropathies, anorectal malformations, Hirschsprung's disease and hypoganglionosis, and, rarely, may follow anorectal sphincter trauma. Historically, incontinence in such children has been managed by means of dietary manipulation, laxatives, suppositories and rectal enemas[1]. While these measures suffice in some cases, a significant proportion of paediatric patients remains incontinent. The introduction of the antegrade continence enema (ACE) procedure has been a major advance[2]. Proponents of the ACE operation report excellent control of faecal continence[2–6]. The aim of this study was to evaluate functional results following the ACE procedure in an effort to help identify factors predictive of outcome.

Patients and methods

All children with faecal incontinence undergoing the ACE procedure between November 1993 and July 1996 were included in the study. Before surgery all children had tried non-operative management with laxatives, suppositories, enemas, manual evacuation and high rectal washouts. A consultant paediatric surgeon and a stoma nurse specialist counselled patients and their families before the ACE procedure. Patients were categorized into four groups according to diagnosis and mobility: (1) ambulant with spinal dysraphism, (2) wheelchair bound with spinal dysraphism, (3) ambulant with miscellaneous disorders and (4) wheelchair bound with miscellaneous disorders.

Operative technique

All patients had routine bowel preparation. Prophylactic antibiotics (cefotaxime and metronidazole) were administered at the time of surgery. In the early part of the study the appendix was reimplanted orthotopically into the caecum with a submucosal tunnel to ensure that it was non-refluxing[2]. Subsequently, the approach was modified to simple appendicostomy, imbricating the caecum around the base of the appendix with interrupted sutures[3]. A skin flap was routinely fashioned at the appendicocutaneous junction to create a wide cutaneous stoma which could be catheterized easily. Tubularized caecum (lateral caecal flap) was employed in children whose appendix had been removed or used in a urological procedure[10]. After operation the stoma was left intubated to 'mature' for 2 weeks using a lubricated Silastic (Dow Corning, Reading, UK) Foley 10–12-Fr catheter[2,4].

Functional assessment

The effectiveness of the procedure was evaluated subjectively using a technical evaluation score and a 'quality of life' improvement (QOLI) score[1,5]. These scores were determined from a questionnaire completed by patients and their parents. The technical score (0–20, where 20 represented the best possible score) addressed the following: (1) degree of postoperative soiling, (2) speed of self-catheterization and (3) time taken to complete the ACE washout. The QOLI score sought to ascertain the child's perception of the effectiveness of the ACE procedure in preventing soiling. Briefly, a score of 5 was ideal or perfect, 4 denoted great improvement but still some problems, 3 was definite improvement but not perfect, 2 showed some improvement, 1 indicated little improvement and 0 was no

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improvement. Continence was defined as less than one episode of soiling per month and 'clean' within 60 min after the ACE washout.

Colonic transit time (CTT) was measured by ingestion of ten radio-opaque marker beads daily with breakfast for six consecutive days. A single plain abdominal radiograph was taken on day 7. CTT was calculated in days by determining the number of markers (M) counted on the radiograph using the formula[7]: CTT = M/10.

Anorectal manometry was performed using a multichannel catheter system (Synectics Medical, Enfield, UK). An open fluid perfusion system was utilized and pressure measured by transducers housed in the perfusion line, in turn connected to a PC Polygraph HR preamplifier (Synectics Medical). An analog–digital converter and personal computer were used to convert the signal to digital values. This permitted measurement of the anorectal resting pressure, squeeze pressure and anorectal reflex[8,9].

Statistical analysis

Data were analysed using SPSS for Windows (v.6. 1.2; SPSS, Chicago, Illinois, USA) and GraphPad Prism (GraphPad Software, San Diego, California, USA). Independent-samples t test with F test for homogeneity of variance and the χ^2 test were used as appropriate. $P < 0{\cdot}05$ was considered significant.

Results

During the study 40 patients (22 girls, 18 boys) underwent the ACE procedure. The causes of faecal incontinence are shown in *Table 1*. Median age at operation was 11 (range 6–21) years. Median duration of follow-up was 21 (range 5–37) months. A completed patient and parent questionnaire was obtained for all children. Six patients declined to undergo estimation of CTT and anorectal manometry studies.

Surgical complications

Five patients had minor wound infections after operation that responded to antibiotic therapy. Eighteen children developed stomal stenosis, seven of whom responded to repeated dilatation. Eleven patients needed formal surgical correction using a V–Y plasty. All patients who had the appendix reimplanted and five of seven of those who had a tubularized caecal flap developed stomal stenosis ($P = 0{\cdot}001$ *versus* simple appendicostomy). Two patients had formal reimbrication of the appendicocaecal junction in an effort to reduce leakage of faeces. Caecal perforation resulting in abdominal pain and peritonitis was encountered in a child following false passage of a catheter. This was explored and repaired surgically. Faecal fistula developed in a further patient who is presently undergoing a trial of non-operative management. Finally, an appendicostomy was converted to a tubularized caecal flap in a child whose abdomen was explored to relieve postoperative adhesion obstruction.

Table 1 Cause of faecal incontinence in 40 patients

Disorder	Wheelchair bound	Ambulant	Total
Spinal dysraphism	14	13	27
Anorectal malformation	1	7	8
Hypoganglionosis	0	3	3
Hirschsprung's disease	0	1	1
Anorectal sphincteric trauma	1	0	1

Table 2 Comparison between wheelchair-bound group with spinal dysraphism and other patients

	Wheelchair bound with spinal dysraphism ($n = 14$)	Others ($n = 26$)
Quality of life improvement (0–5)*	2·5 (1–5)†	4 (2–5)
Colonic transit time (days)*	2·6 (0·3–6·0)	1·9 (0·2–5·3)
Anorectal resting pressure (mmHg)*	48 (29–89)	42 (27–109)
Anorectal squeeze pressure (mmHg)*	0 (0–157)†	91 (0–202)
Continent	7‡	21
Reversal	2	2

*Values are median (range). †$P < 0{\cdot}05$ (t test); ‡$P < 0{\cdot}05$ (χ^2 test)

Functional outcome

The ACE procedure was reversed in four children (three had spina bifida, two of whom were wheelchair bound; one had a failed revisional posterior sagittal anorectoplasty) within 5–19 months because of uncontrollable faecal soiling following operation (*Table 2*). Three of these patients now have a permanent colostomy and the other reverted to a regimen of rectal enemas and manual evacuation. These patients did not participate in the functional study. Eight further patients, five who were wheelchair bound with spinal dysraphism, two who were ambulant with myelomeningocele and one who was ambulant with tethered cord and lipomeningocele, were classed as incontinent following the ACE procedure, giving an overall success rate of 28 of 40 children. The mean QOLI score was 3·5 and all children remaining with an ACE stoma reported some improvement in quality of life. QOLI scores were significantly lower in the group of patients with spinal dysraphism who were wheelchair bound than in all other groups ($P = 0{\cdot}033$, t test); there were no significant differences between the two groups of ambulant patients and the wheelchair-bound group with miscellaneous disorders. Only seven of 14 patients who were wheelchair bound with spinal dysraphism were continent following the ACE procedure, compared with 21 of the other 26 patients ($P = 0{\cdot}016$, t test).

Maximal anorectal squeeze pressure was significantly lower in the patients with spinal dysraphism who were wheelchair bound than in all other groups ($P = 0{\cdot}0006$) (*Table 2*). Overall, in this series seven of eight children classified as incontinent after operation had no anorectal squeeze pressure ($P = 0{\cdot}0014$ *versus* all other continent patients ($n = 28$), χ^2 test).

There were no differences in CTT or technical evaluation scores between patient groups or when children were classified according to functional outcome. There were no significant differences in technical evaluation score, QOLI score and continence rates when patients were analysed according to the nature of the surgical procedure performed (*Table 3*).

Enema technique

The majority of the children administer the ACE enema on alternate days. In 22 patients a phosphate enema followed by a saline washout has proved satisfactory. Judicious use of liquorice stick with saline, saline alone, Microlax (Evans Medical, Leatherhead, UK) and Picolax

Table 3 Comparison between different surgical techniques

Surgical technique	No. of patients	Technical evaluation score*	QOLI score*	Continent
Appendicostomy	23	16 (11–20)	3 (1–3)	17
Tubularized caecal flap	7	13 (9–16)	2 (1–4)	5
Orthotopic reimplantation of appendix	6	15 (12–19)	2 (2–4)	6

*Values are median (range). QOLI, quality of life improvement

(Ferring, Feltham, UK) is useful in five patients who have developed adverse reactions to phosphate. Two patients who experienced abdominal cramps following the enema responded adequately to the use of proprietary antispasmodic (Buscopan; Boehringer Ingelheim, Bracknell, UK) and motility (Lomotil; Searle, High Wycombe, UK) agents.

Discussion

Faecal incontinence in a child is a significant psychosocial handicap. Previously there were few options available when standard techniques of dietary manipulation, laxatives and enemas failed. Many of these children were condemned either to a lifetime of faecal incontinence and pads or to faecal diversion with a colostomy. In 1990, Malone *et al.*[2] pioneered the ACE procedure. The rationale behind this operation is simple: 'to provide patients with a continent catheterisable colonic stoma' so that they can remain clean and independent[2]. The ACE operation has now been offered to a variety of patients with faecal incontinence, and proponents report excellent control of the incontinence[2–6].

In the present study early failure (persistent faecal incontinence) occurred in four of 40 patients, prompting critical appraisal of the authors' institutional experience with the ACE procedure. Three of these patients had spina bifida, two of whom were confined to wheelchairs; the other patient had a revisional posterior sagittal anorectoplasty. Further analysis revealed a significantly poor functional outcome for wheelchair-bound patients with spinal dysraphism. Only seven of 14 of these children derived benefit (i.e. are rendered clean) from an ACE operation. The reasons for failure were apparent on scrutinizing the anorectal manometry profiles of these patients. Overall, maximum anorectal squeeze pressures were significantly lower in the wheelchair-bound patients with spinal dysraphism, and in seven of eight of these children who were incontinent following the ACE operation no squeeze pressure could be recorded. This led to persistent and involuntary episodes of faecal soiling despite numerous efforts to adjust or tailor enema schedules to individual needs. Of interest was the fact that seven of these patients who did have an element of squeeze pressure activity could be made clean. Three other patients remained incontinent by the reported criteria, although one had an improved QOLI score. All of these children had some form of spinal dysraphism: two were ambulant with myelomeningocele and no squeeze pressure, and one was ambulant with lipomeningocele and tethered cord.

Surgical complications were not infrequent. Stomal stenosis occasionally responded to dilatation, although 11 of 18 affected patients required a V–Y plastic revision. These problems were significant in children who had orthotopic reimplantation or a tubularized caecal flap[2,10] and are less frequent now that appendicostomy with caecal imbrication is performed[3,4]. A button caecostomy device is a new alternative[12]. Children and their parents must be given instructions on signs and symptoms that herald viscus perforation and enema toxicity[11]. Close communication between the patient, parents, nurses and surgical staff reinforces these issues.

The ACE operation in selected patients may have a 70 per cent success rate in achieving faecal continence. Caution should be exercised when offering this procedure to patients who are wheelchair bound with spinal dysraphism who, at best, achieve a 50 per cent continence rate. Absent anorectal squeeze pressure is a poor prognostic indicator.

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Laparoscopy in the management of the impalpable undescended testis

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Background This study evaluates the role of laparoscopy for managing the intra-abdominal testis.

Methods Over 30 months, 48 children (six with previous groin explorations) underwent laparoscopy for a unilateral impalpable undescended testis. The patients' age ranged from 1 to 9 years.

Results Eleven children required insertion of 'working ports' for mobilization of obscuring colon before the diagnosis could be established. Twenty-eight children had an absent testis. In nine, vas and vessels entered the internal ring. In 19, vas and vessels ended blindly above the internal ring. Twenty children had an intra-abdominal testis. Ten underwent a laparoscopic single-stage orchidopexy (eight without and two with ligation of vessels); at a minimum follow-up of 2 years, one testis in this group had atrophied, three were located in the lower half of the scrotum and six in the upper half. The remaining ten children underwent a laparoscopic two-stage Fowler–Stephens operation. At a minimum follow-up of 6 months, eight of these testes were palpable in the lower half and two in the upper half of the scrotum.

Conclusion In the majority of cases, laparoscopy obviates the need for groin exploration. Technically a first-stage Fowler–Stephens procedure can be performed easily and effectively via the laparoscope. However, the second-stage Fowler–Stephens procedure or single-stage orchidopexy requires laparoscopic skills and may not necessarily provide sufficient length to the testicular attachment.

Cryptorchidism affects 0·8 per cent of male children at 1 year of age[1]. In approximately 20 per cent of these children the testis will be impalpable and presumed to be located within the abdominal cavity[1,2]. Although ultrasonography, computed tomography and venography have been used[3], laparoscopy is the most reliable method of confirming the presence of an intra-abdominal testis[4–10]. Following localization of an intra-abdominal testis an open procedure, one-stage orchidopexy, one- or two-stage Fowler–Stephens procedure or microvascular transfer, is required for placement of the testis within the scrotum[11]. Alternatively the testis is removed.

Therapeutic laparoscopy is beginning to be used in the management of intra-abdominal testes[9,10,12–16]. This report describes present experience in assessing the role of laparoscopic surgery in the management of the impalpable undescended testis.

Patients and methods

Over 30 months, 48 children underwent laparoscopy for evaluation of a unilateral impalpable testis following careful palpation of the scrotum and groin under general anaesthesia. Six of the patients had undergone a negative groin exploration at other institutions. The mean age of the patients was 3·3 (range 1–9) years. Informed consent was obtained for laparoscopy with permission to proceed with orchidectomy, one- or two-stage orchidopexy or groin exploration depending on the findings at laparoscopy.

Under general anaesthesia the abdomen was palpated to ensure that the bladder was empty. A primary periumbilical port (3·5–10 mm) was inserted using an open technique[17] and a pneumoperitoneum created using carbon dioxide with a flow rate of 0·2 l/min and an intra-abdominal pressure of 6–8 mmHg. Following exploration of the abdominal cavity in a Trendelenberg position, with or without a lateral tilt, the sites (usually high iliac/low lumbar region and suprapubic/opposite iliac region) and sizes (3·5–10 mm) of one or two working ports were selected depending on the child's size, laparoscopic findings and the type of procedure required.

When the testis was low with a reasonably long vascular pedicle, single-stage orchidopexy was attempted with complete mobilization of the testicular attachment from the lower pole of the kidney to the base of the bladder. The mobilized testis was then placed through the inguinal canal and secured in a dartos pouch with or without groin incision. Following early experience with this technique, single-stage orchidopexy was converted to a one-stage Fowler–Stephens procedure (division of testicular vessels and orchidopexy at the same time) when the vascular pedicle was too short to allow testicular positioning in the lower half of the scrotum.

In children undergoing a two-stage Fowler–Stephens procedure a first stage (division of testicular vessels) was performed with laparoscopic ligation of the testicular vessels using two metal clips or non-absorbable suture ligatures. Subsequently a lararoscopic second-stage procedure (mobilization of testis and orchidopexy) was done 6–9 months later.

Results

Following initial laparoscopy, 11 children required insertion of one or two working ports for mobilization of the colon or division of adhesions to establish the diagnosis. Twenty-eight children had an absent testis on the side under investigation. In 19, the vas and vessels were seen to end blindly above the internal ring. In the remaining nine, vas and vessels entered the inguinal canal and groin exploration was performed. Histological evaluation of tissue excised from the end of the attenuated spermatic cord confirmed the presence of the vas deferens but did not identify any testicular tissue.

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Twenty children had an intra-abdominal testis. Of these, ten underwent a single-stage laparoscopic orchidopexy (eight without and two with division of the testicular vessels). At follow-up (mean 2·5 (range 2–4) years), three testes were located in the lower half of the scrotum and six in the upper half. One high testis managed by extensive mobilization with division of the testicular vessels had atrophied. The remaining ten children underwent a laparoscopic two-stage Fowler–Stephens procedure and at subsequent follow-up (mean 1·5 (range 0·5–3·5) years) eight testes were located in the lower half and two in the upper half of the scrotum.

The mean operating time was 18 (range 15–40) min for laparoscopy alone, 30 (range 22–60) min for a first-stage Fowler–Stephens procedure and 65 (range 52–90) min for single-stage orchidopexy and second-stage Fowler–Stephens operation. All children who had laparoscopy alone or a first-stage Fowler–Stephens procedure were managed as day cases. Children undergoing orchidopexy either as single-stage procedure or second-stage Fowler–Stephens operation stayed in hospital overnight but none required opiate analgesia. There were no technical failures and no laparoscopy-related complications.

Discussion

The risks of atrophic change and malignancy developing within an undescended testis are widely recognized[18,19], as is the role of laparoscopy in identification of the intra-abdominal testis[4–10]. It has been reported that single-port diagnostic laparoscopy fails to obtain the correct diagnosis in 5–8 per cent as a result of bowel or adhesions obscuring the testis or its attachments[7,8,20]. Laparoscopic examination should include complete visualization of the pelvis and retroperitoneum behind the colon. It is therefore not surprising that in this series a high proportion of children (11 of 48) required insertion of one or two additional laparoscopic ports. In the six children who had previous groin exploration elsewhere, laparoscopy demonstrated that the testis was absent in four and in two it was located within the abdominal cavity. Diagnostic laparoscopy should be 100 per cent accurate in the hands of an experienced laparoscopic surgeon. The value of groin exploration when vas and vessels enter the inguinal canal in the absence of a palpable testis is uncertain as testicular tissue is rarely found.

Operative laparoscopy is becoming increasingly common and recent reports of orchidopexy and first-stage Fowler–Stephens operation suggest that the technique may be used as an alternative to open surgery for definitive management of the intra-abdominal testis[9,10,12–16]. The present experience supports that of Nassar[12] and suggests that a first-stage Fowler–Stephens orchidopexy can effectively be performed via the laparoscope. The technique, however, requires three laparoscopic ports.

Single-stage orchidopexy and second-stage Fowler–Stephens procedures are conventionally carried out via a groin incision. Using a laparoscopic approach, the mobilized testis can be pulled into the scrotum via the incision used to create a dartos pouch[21]. This technique requires extensive laparoscopic experience. The role of single-stage laparoscopic orchidopexy remains uncertain as even following extensive mobilization it is frequently not possible to gain sufficient length of vascular pedicle to ensure that the testis remains located in the lower half of the scrotum. This was less of a problem in children undergoing a Fowler–Stephens orchidopexy.

Laparoscopic orchidectomy is seldom necessary[9,10,14,22]; it was not required in any of the children in this series. However, if orchidopexy is considered unsuitable, laparoscopic orchidectomy can be done.

In this study the success of laparoscopic orchidopexy for intra-abdominal testes as judged by placement of the testis within the scrotal sac was high (19 of 20 testes). This compares well with the results of open surgical techniques: 67 per cent for one-stage Fowler–Stephens, 77 per cent for staged Fowler–Stephens, 81 per cent for intra-abdominal orchidopexy and 84 per cent for microvascular transfer[11].

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Stimulation of inflammatory markers after blunt trauma

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Background Inflammatory mediators are released after trauma and may be related to the pathogenesis of sepsis. A prospective combined study of the pattern of release of an inflammatory mediator, interleukin (IL) 6, leucocyte activation (polymorphonuclear leucocyte (PMN) CD11b receptor expression and plasma elastase-α_1 proteinase inhibitor complex (E–α_1PI)) and soluble endothelial adhesion molecule expression (soluble E-selectin (sE-selectin) and soluble intracellular adhesion molecule 1 (sICAM-1)) was performed in patients suffering blunt trauma without adult respiratory distress syndrome (ARDS) or multiple organ failure syndrome (MOFS).

Methods Thirty-one patients with a mean Injury Severity Score (ISS) of 14 (range 9–57) were studied. Venous blood samples were collected within 6 h of injury and then at 1, 3, 5 and 7 days. Leucocyte CD11b expression was quantified by flow cytometry. Serum IL-6, plasma E–α_1PI, sE-selectin and sICAM-1 were measured by enzyme-linked immunosorbent assay.

Results Serum IL-6, CD11b expression and E–α_1PI levels were significantly raised above control values ($P<0{\cdot}0001$) on admission, slowly returning towards control values over the study period (median IL-6, 140 pg/ml *versus* undetectable; CD11b, 14·8 *versus* 6·4 mean channel fluorescence units; E–α_1 PI, 208 *versus* 52 μg/l). The sICAM-1 level rose to a median of 539 ng/ml at 5 days (control 243 ng/ml). The median sE-selectin level also progressively increased to a maximum level of 80 ng/ml at 5 days (control 49 ng/ml). Eleven patients developed postoperative sepsis. Significant differences in CD11b expression were seen at days 3, 5 and 7 and in E–α_1 PI at 6 h, 24 h and 3 days in patients who subsequently developed sepsis ($P<0{\cdot}05$). Severe injury (ISS 16 or greater) was associated with significantly greater responses in these measurements.

Conclusion These data show that markers of inflammation are specifically stimulated by trauma even when ARDS and MOFS do not occur. The CD11b receptor on PMNs may be useful in screening patients destined to develop post-traumatic sepsis.

Multiple organ failure syndrome (MOFS) is a leading cause of death in patients after multiple trauma. This has been associated with an exaggerated systemic inflammatory response syndrome which may occur after trauma and may lead to critical organ injury[1]. Several components of the immune system have been implicated in this process including the release of proinflammatory cytokines, activated polymorphonuclear leucocytes (PMNs) and leucocyte–endothelial interactions[2]. The role of each of these elements is not clear although many consider the neutrophil as the pivotal player in the pathogenesis of adult respiratory distress syndrome (ARDS) and MOFS and the expression of cell surface receptors on neutrophils to be regulated by proinflammatory cytokines[3–9]. However, a specific inflammatory marker has not yet been implicated in the process underlying the development of MOFS.

The proinflammatory cytokine interleukin (IL) 6 is produced by a variety of cells such as monocytes, macrophages, lymphocytes, fibroblasts and endothelial cells[10,11]. IL-6 is involved in the modulation of local inflammation and the systemic reaction known as the acute-phase response which is characterized by fever, leucocytosis, tachycardia, net catabolism and alteration in the production of hepatic proteins[12].

Activated leucocytes express surface glycoproteins known as integrins, of which the β_2 integrins are particularly important[13]. These consist of a β_2 (CD18) chain covalently linked to one of three different α chains (CD11a, CD11b, CD11c). The CD11b/CD18 receptor binds complement and has a major role in neutrophil adhesion and diapedesis[14]. PMN–endothelial cell adhesion involves intracellular adhesion molecule (ICAM)1 and E-selectin[15,16], the E-selectin initiating and ICAM-1 completing the adhesion process which allows migration of the neutrophils across the vascular endothelium[17], where final tissue destruction involves the release of elastase from PMNs[18]. Elastase degrades elastin, collagen, proteoglycans and fibronectin[19] and measurement of complexed neutrophil elastase provides a sensitive indicator of neutrophil activation.

The purpose of this investigation was to study changes which occur in serum IL-6, plasma elastase–α_1 proteinase inhibitor complex (E–α_1PI), neutrophil CD11b receptor expression, serum soluble ICAM-1 (sICAM-1) and soluble E-selectin (sE-selectin) levels to determine the relationship between these aspects of the inflammatory process in a series of patients suffering blunt orthopaedic trauma, who did not develop ARDS or MOFS but did develop sepsis.

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Table 1 Numbers of septic complications related to the injuries sustained

Injuries	No. of patients	Median (range) ISS	Infective complications
Fractured pelvis*	9	18 (9–27)	4
Fractured femur*	14	14 (9–57)	5
Fractured tibia*	7	9 (9–10)	1
Fractured forearm*	1	11	1

*Other injuries sustained. ISS, Injury Severity Score

Patients and methods

Thirty-one adult patients were studied prospectively following blunt trauma. All patients arrived in hospital within 6 h of injury, had an Injury Severity Score (ISS) of 9 or more and were subsequently in hospital for at least 7 days. *Table 1* shows the patients' characteristics and the injuries sustained with the corresponding ISS. For comparison the patients were divided into two groups: a severely injured group with an ISS of 16 or more, and a group with moderate injury and an ISS of 9–15, as defined by Ertel *et al.*[20]. Patients were defined as developing sepsis if a systemic response to infection was clinically evident (i.e. two or more of the following: peripheral white blood cell count of less than 2×10^9 per litre or more than 15×10^9 per litre; temperature higher than 38°C; twofold increase in serum alkaline phosphatase level; bilirubin level higher than 20 μmol/l; hypotension, with systolic blood pressure less than 100 mmHg for 2 h; and tachycardia greater than 100 beats per min for 2 h), along with a clinical evidence of an infection site supported by a positive bacterial culture[21]. Ethics committee approval was obtained and all patients or their representatives gave oral or written consent.

Venous blood samples were collected on arrival in the emergency department and at 1, 3, 5 and 7 days following injury. Similarly, venous blood samples were collected from 20 (11 women and nine men) healthy uninjured individuals, with a median age of 54 (range 23–85) years who formed the control group for this study. The serial venous blood samples were collected on ice into two types of endotoxin-free vacutainer tubes, one containing ethylenediamine tetra-acetic acid (EDTA) and one containing clot activator. Processing took place within 2 h of collection. The tubes containing the clot activator were centrifuged at 1000 r.p.m. (MSE; Scientific Instruments, Crawley, UK) for a period of 10 min, the serum and plasma were collected and stored at −70°C. Flow cytometric studies were performed on 100 μl blood from the EDTA tube.

Flow cytometry of polymorphonuclear leucocytes

Polymorphonuclear cells were stained with fluorescent labelled antibodies against CD11b in a whole blood assay as described previously[22]. An isotype-matched fluorescein isothiocyanate-conjugated monoclonal antibody that does not specifically react with human cells was used as a negative control to exclude any non-specific Fc-related antibody binding.

Immunofluorescence was determined on a Coulter Epics (Luton, UK) flow cytometer. Forward angle and 90° light scatter measurements were collected. At least 10 000 events were counted on each sample within a region gated for PMNs. The data were analysed using the Coulter Epics XL cytometer software and expressed in mean channel fluorescence units.

Determination of inflammatory markers

Serum IL-6, s-ICAM and sE-selectin levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (R and D Systems, Minneapolis, Minnesota, USA). All measurements were performed in duplicate. Plasma E-α_1 PI levels were determined using an indirect sandwich ELISA assay[23] recalibrated against the currently commercially available Merck elastase assay.

Statistical analysis

Non-parametric tests (Mann–Whitney *U* test) were used to assess differences between observed values, and area under the curve (AUC). Differences were considered significant at $P < 0{\cdot}05$.

Results

Serum IL-6, plasma E-α_1PI levels and CD11b expression in patients were significantly raised above control levels ($P < 0{\cdot}0001$) on admission slowly returning towards control values over the study period (*Figs 1*, *2* and *3*). The sICAM-1 and sE-selectin levels were slightly raised initially and increased with time. This rise was initially not significantly above control values but became significant after day 3.

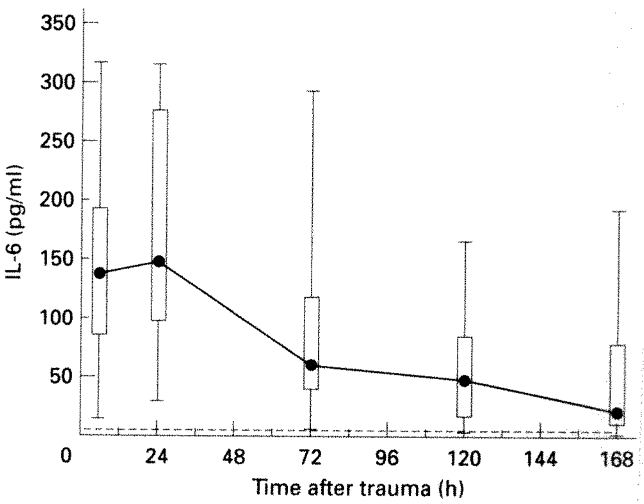

Fig. 1 Interleukin (IL) 6 concentrations with time following trauma ($n = 31$). Median values (dots), interquartile ranges (boxes), and the maximum and minimum values (bars) are shown. The 95 per cent cut-off for the control group is represented by the dotted line

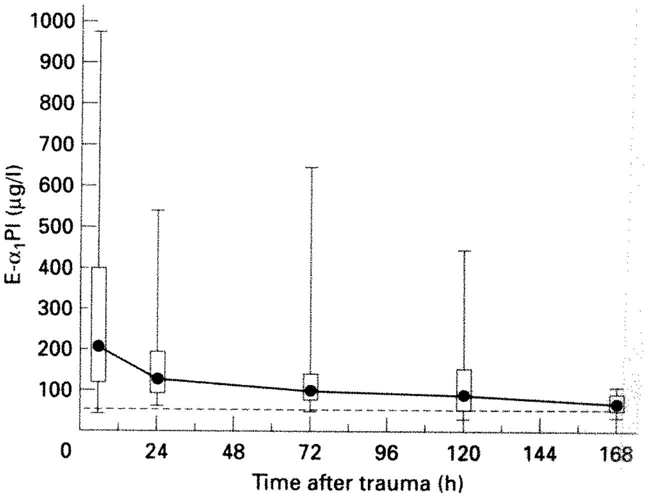

Fig. 2 Elastase –α_1 proteinase inhibitor (E–α_1 PI) concentrations with time following trauma ($n = 31$). Median values (dots), interquartile ranges (boxes), and the maximum and minimum values (bars) are shown. The 95 per cent cut-off for the control group is represented by the dotted line

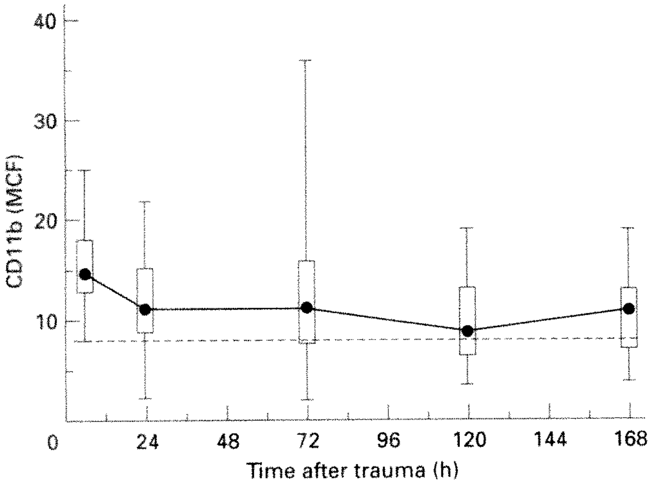

Fig. 3 Polymorphonuclear leucocyte CD11b mean channel fluorescence (MCF) with time following trauma ($n = 31$). Median values (dots), interquartile ranges (boxes), and the maximum and minimum values (bars) are shown. The 95 per cent cut-off for the control group is represented by the dotted line

Effect of sepsis

Eleven of the 31 patients developed sepsis during the course of the study. However, none of the patients studied developed MOFS. There were no significant differences in sE-selectin, sICAM-1 or IL-6 concentrations between patients with and without sepsis at any time. A significant difference in the expression of CD11b was observed in patients with sepsis at 3, 5 and 7 days of the study period (Mann–Whitney *U* test, $P = 0{\cdot}01$) (AUC, $P = 0{\cdot}04$). The E-α_1 PI level appeared to be higher in patients with sepsis than in those without sepsis during the first 3 days of the study period (Mann–Whitney *U* test, $P < 0{\cdot}05$) but this difference was lost over the subsequent 7 days (AUC, $P = 0{\cdot}1$) (*Fig. 4*). There was no difference in ISS between the patients with and without sepsis ($P = 0{\cdot}109$).

The effect of Injury Severity Score

The results were further analysed according to ISS. Two groups of patients were identified. Group A consisted of ten patients with an ISS of 16 or more and group B of 21 patients with an ISS of 15 or less. The release of plasma E–α_1 PI differed significantly between the two groups at all time points with the more severely injured group (A) having significantly higher levels. A similar difference was also seen for serum IL-6 (data not shown). The difference between the two groups in terms of levels of adhesion molecules sICAM-1 and sE-selectin (higher in group A) was significant at day 5 (sICAM-1 and sE-selectin) and day 7 (sICAM-1). However, no significant difference between the two groups was seen in the leucocyte expression of CD11b.

Discussion

It is now believed that an exaggerated systemic inflammatory response may be responsible for the development of MOFS after trauma. However, although many inflammatory mediators have been implicated in this process the overall picture and the key elements remain uncertain. No studies have yet examined a number of elements of each stage of this process from cytokine to neutrophil elastase release in a single group of patients. This study aimed to obtain baseline data on trauma patients who developed a sepsis response although clearly no conclusions can be reached about MOFS from the present data.

The proinflammatory cytokine IL-6 was found to be released rapidly after trauma at levels which were significantly greater in more seriously injured patients. These findings parallel those reported after elective surgery[24] and confirm those of Cruickshank and associates[25] and Hoch *et al.*[26]. Serum concentration of IL-6 therefore represents a sensitive marker of tissue damage and may play an important role initiating the systemic inflammatory response syndrome. The serum IL-6 level was not

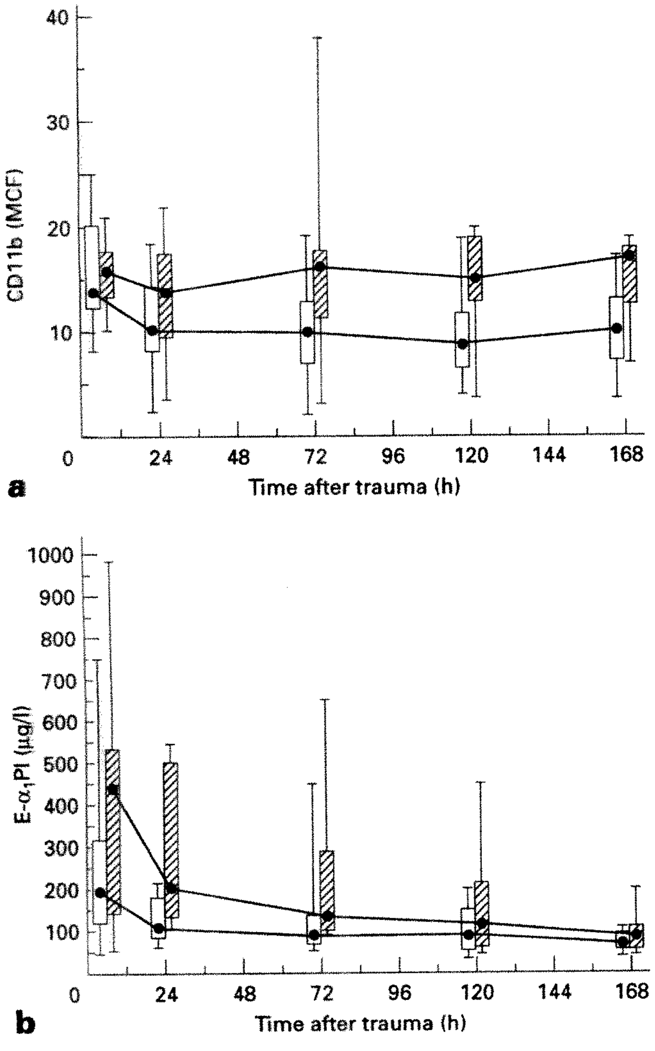

Fig. 4 **a** Polymorphonuclear leucocyte CD11b mean channel fluorescence (MCF) and **b** elastase-α_1 proteinase inhibitor (E–α_1 PI) concentrations with time following trauma in 31 patients subdivided on the basis of development of sepsis ($n = 11$; ▨) or no sepsis ($n = 20$; ☐). Median values (dots), interquartile ranges (boxes), and the maximum and minimum values (bars) are shown. $P = 0{\cdot}04$ (CD11b), $P = 0{\cdot}1$ (E–α_1 PI) (area under the curve) associated with sepsis in this study, although others have found that increased serum levels of IL-6 correlated with a poor outcome in patients with sepsis[27].

In this study the effect of trauma on neutrophil activation was assessed by studying the expression of CD11b surface receptor and measurement of plasma elastase. The levels of the CD11b surface receptor were found to be significantly raised on admission. The degree of upregulation did not correlate with the ISS but was significantly higher in patients who developed septic complications. This finding parallels that of the effects of elective major resectional surgery on neutrophil CD11b expression[22]. Post-traumatic MOFS has also been associated with increased number of CD11b/CD18 receptors on the PMN surface and an upregulation of the oxidative burst[28]. In this study, there was no apparent relationship between neutrophil CD11b expression and sepsis until the third day after injury when the infection was presumably establishing itself in the tissues.

A significantly raised E-α_1PI level was observed on admission which seemed to be higher in those with greater degrees of injury and with the development of sepsis, being significantly raised at day 1 and day 3 compared with that in patients without sepsis. One other study has reported a similar pattern of elastase release but was unable to correlate this with injury severity, probably because of the small group of patients studied[29]. Repetitive increases of plasma elastase have been seen after trauma in patients who developed MOFS[30] although, interestingly, this was also associated with septic complications. Nuytinck *et al.*[31] also reported that raised plasma levels of elastase correlated well with the severity of injury and the occurrence of multiple organ failure. Moreover, these authors were also able to discriminate between later survival or death at an early stage in the clinical course using this parameter. The present data also suggest that significantly raised levels of plasma Eα_1PI may have predictive value on days 1 and 3 for the subsequent development of sepsis syndrome.

Endothelial adhesion molecule expression is also essential for leucocyte adhesion and migration. Both sE-selectin and sICAM-1 levels were found to be raised significantly in the plasma by day 3 following traumatic injury and subsequently increased, the magnitude of the increase being related to the degree of injury. Law *et al.*[32] found a significant correlation between the raised levels of sICAM-1 and the later occurrence of and severity of multiple organ failure but the present study did not show a relationship between sICAM-1 and the occurrence of septic complications.

The data from this investigation confirm that early following trauma, IL-6 is released and neutrophils are activated. Soluble endothelial adhesion molecules were subsequently detectable in the peripheral blood suggesting that receptor–ligand binding between neutrophils and endothelial cells may have occurred. The magnitude of these responses is related to the degree of trauma sustained and some are associated with the subsequent development of sepsis. It is probable that loss of control of this normal inflammatory response syndrome with overstimulation of the parameters involved may be responsible for the widespread tissue damage characteristic of ARDS and MOFS often seen in multiply injured patients. There may be an idiosyncratic genetically determined component of the response to injury which in some individuals results in loss of the normal control mechanisms that attenuate this response, thus allowing it to proceed to widespread tissue injury, clinically manifest as ARDS and MOFS. Indeed, there is now preliminary evidence that the polymorphic expression of another neutrophil receptor, CD16, may be related to the degree of the sepsis response[33].

Activation of the inflammatory processes as suggested by an increase in the level of these markers is the norm even in patients who do not develop ARDS or MOFS, as seen in the present study. Further studies are now required on the input of trauma on the production of negative regulatory cytokines such as IL-10 which has been shown to be upregulated after major surgery[34].

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Sentinel node localization in patients with breast cancer

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Background Intraoperative lymphatic mapping and identification of the first draining lymph node (the sentinel node) may allow some patients with breast cancer to avoid the morbidity of formal axillary clearance. The aim of this pilot study was to establish the reliability of the technique in predicting axillary node status.

Methods Sixty-eight consecutive patients with breast cancer, 38 undergoing mastectomy and 30 wide local excision, were included. Some 2–4 ml of 2·5 per cent Patent Blue dye was injected into adjacent breast tissue on the axillary side of the primary tumour. After 5–10 min, the axilla was explored. Blue-stained lymphatics were dissected to the sentinel node, which was removed for frozen-section examination, followed by routine histology. Formal axillary dissection was then completed.

Results A sentinel lymph node was identified successfully in 56 (82 per cent) of 68 patients. Histology of the sentinel node accurately predicted axillary node status in 53 (95 per cent). There were three false negatives (5 per cent). In each case, only a single non-sentinel node was tumour positive. Sensitivity and specificity were 83 and 100 per cent respectively.

Conclusion This technique would allow a selective policy of formal axillary dissection in only node-positive patients; however, further experience and refinement are needed.

Axillary node status remains the most important prognostic factor in breast cancer. Formal axillary clearance has remained the best method of breast cancer staging. There is no other reliable method of identifying lymph node-negative patients, using either imaging techniques[1] or pathological characteristics of the primary tumour[2].

Although there is no doubt about the prognostic importance of lymph node status, there is controversy over the extent of axillary surgery required. Axillary dissection is associated with significant morbidity[3,4]. Limited dissection has a lower incidence of morbidity than complete level III axillary clearance. However, axillary node biopsy or sampling has a staging error of 0–42 per cent[5–8] and an increased incidence of axillary recurrence[7,8]. A lower, level II dissection has a staging error of only 2–3 per cent[9,10], and this procedure is preferred by many surgeons.

An alternative strategy of lymph node staging, involving intraoperative lymphatic mapping and identification of the first draining node (the sentinel node), is established in the management of malignant melanoma[11]. Histological evaluation of the sentinel node when compared with the complete lymphatic field shows a high correlation and only a 1 per cent false-negative rate. Preliminary work by Giuliano *et al.*[12,13], using blue dye, suggested that this technique may be applicable to breast cancer. An alternative technique using radiolabelled colloid and a hand-held γ probe has been reported, with similar encouraging results[14,15].

This was a pilot study to verify the reliability of sentinel node localization in predicting axillary nodal status and to carry out a cost analysis in comparison with formal axillary dissection.

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Patients and methods

The study design is summarized in *Fig. 1*. Sixty-eight consecutive patients with primary invasive breast cancer were included. Mean age was 62 (range 33–86) years. Thirty-eight patients underwent mastectomy and 30 wide local excision, in conjunction with axillary exploration. Informed consent was obtained from all patients.

Intraoperative lymphatic mapping involved injection adjacent to the tumour of 2–4 ml 2·5 per cent Patent Blue dye (Laboratoire Guerbet, Aulney-Sous-Bois, France). After 5–10 min the axilla was explored and the lymphatics were identified and dissected to the sentinel node. An effort was made to ensure that the first draining node had been identified by retrograde dissection of the lymphatic track to the tail of the breast. The sentinel node was removed for immediate frozen-section examination, followed by paraffin-section histology (*Fig. 2*). Formal axillary clearance was then completed. In patients who had a wide local excision, this was carried out through a separate incision. In patients who had a mastectomy, the standard incision

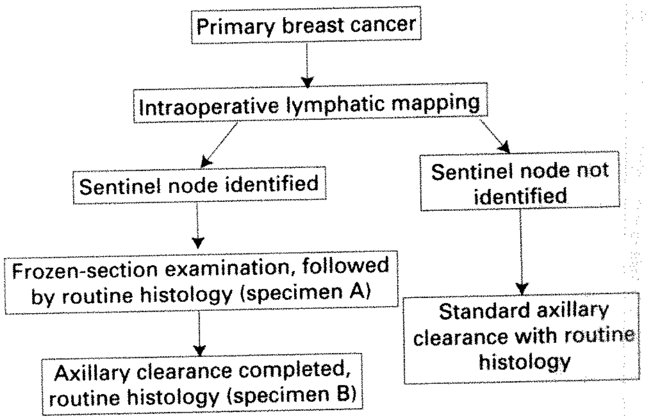
Primary breast cancer
Intraoperative lymphatic mapping
Sentinel node identified
Sentinel node not identified
Frozen-section examination, followed by routine histology (specimen A)
Standard axillary clearance with routine histology
Axillary clearance completed, routine histology (specimen B)

Fig. 1 Design of study to compare intraoperative lymphatic mapping and sentinel node histology with formal axillary dissection in the axillary staging of breast cancer

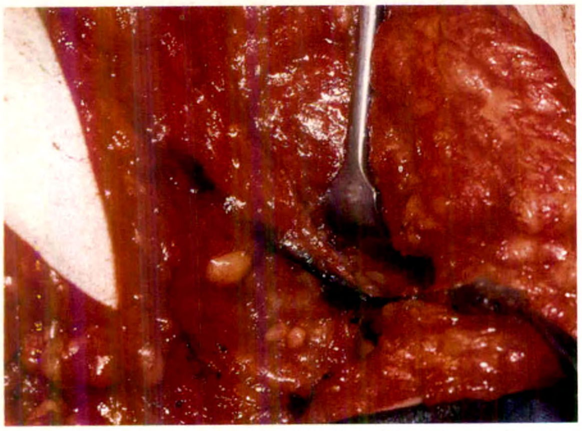

Fig. 2 Intraoperative lymphatic mapping. The blue-stained lymphatic track can be seen leading to the sentinel node, which has been dissected from surrounding fat and is held in dissecting forceps (bottom right). This patient then had a mastectomy

was made and inferior and superior skin flaps were dissected before lymphatic mapping.

All axillary lymph nodes were processed individually for histological examination by a consultant pathologist with a special interest in breast cancer. A full record of operating theatre time was kept to facilitate a cost analysis.

Results

Twenty-one patients (31 per cent) had involved axillary nodes on histology and 47 (69 per cent) were node negative.

Sentinel nodes were identified successfully in 56 patients (82 per cent). In 12, there was more than one sentinel node; a total of 69 was identified.

The histological status of the sentinel node predicted axillary node status accurately in 53 (95 per cent) of 56 patients. There were three false negatives; sensitivity and specificity were 83 and 100 per cent respectively. In five patients the sentinel node was the only positive node recovered from the axilla.

Immediate frozen-section examination of the sentinel node accurately predicted the paraffin-section histology in 53 (95 per cent) of 56 patients. In two patients with positive sentinel nodes, the frozen section was reported as suspicious of metastatic carcinoma. In one, a sentinel node was negative on frozen-section examination, but a single tumour deposit was identified on paraffin section. If formal axillary clearance had been performed on the basis of sentinel node histology, a single patient would have required a second procedure.

Cost analysis

The mean time to dissect and remove the sentinel node was 8 (range 1–18) min compared with 40 (range 20–70) min to complete the axillary dissection. The authors' average theatre costs are £432 per hour. The respective costs of operating time per patient are shown in *Table 1*.

Pathology costs were £95 for frozen section and subsequent histology on the sentinel node, compared with £70 for routine processing of lymph nodes recovered from the axillary dissection specimen.

If sentinel node localization had been used as a staging procedure and a selective policy of formal axillary dissection employed only in node-positive patients, the total operating cost would have been £32 659 compared with £42 106 if routine axillary dissection had been carried out. The respective pathology costs were £7210 and £4760. The combined costs for sentinel node localization were £39 869 compared with £46 866 for routine axillary dissection. The technique of sentinel node localization could have saved £6997 or 15 per cent.

Table 1 Operating time and costs

	Sentinel node localization	Axillary dissection	Total time in operating theatre
Mean (range) theatre time (min)	8 (1–18)	40 (20–70)	86 (60–105)
Cost per patient (at £432 per h)	£57·60	£288·00	£619·20

Discussion

Axillary lymph node dissection is an important staging procedure and has a therapeutic role in reducing the risk of axillary relapse[16]. It is, however, associated with significant morbidity. Seromas requiring aspiration occur in 30–42 per cent of cases[17,18]. Ivens *et al.*[4] found subjective morbidity, interfering with daily living, in 39 per cent of 126 women surveyed 6 months after full axillary clearance.

Reliable prediction of axillary node metastases could help to avoid routine axillary dissection in some patients with invasive breast cancer. However, non-invasive methods have been unsuccessful. Clinical examination[19] and imaging techniques such as ultrasonography, computed tomography and lymphoscintigraphy have largely failed as reliable methods of detecting axillary disease[1].

Limited dissection is an alternative to axillary clearance. In the Edinburgh randomized trial of axillary sampling or clearance[8], a subgroup of 67 patients in whom axillary sampling was performed subsequently went on to have axillary clearance. Twenty-six (39 per cent) had histologically positive nodes and in each case these had been identified on sampling. This contrasts with the results from other studies, showing a staging error rate of 8–42 per cent[5–7]. In one of these studies, involving 473 patients with stage I or II disease, no nodes were identified for histological examination after axillary sampling in 116 patients (25 per cent)[7]. There is conflicting evidence on the value of the qualitative information obtained from axillary sampling. In addition, sampling may not give accurate information on the number of involved nodes, which influences prognosis and often determines the use of adjuvant systemic therapy.

Sentinel node biopsy seems to have sufficient reliability to allow formal axillary clearance to be limited to node-positive patients. Successful lymphatic mapping and localization of the sentinel node is possible in a large proportion of patients and the histology of the sentinel node is highly predictive of axillary node status.

There were three false negatives in this series. However, this rate is low and close to the figure reported for level I and II axillary dissection[9,10]. In each patient only a single non-sentinel lymph node was tumour positive, and in one a micrometastasis was the only evidence of involvement.

This technique is also cost effective. In addition to the saving in operating time and cost, a reduced inpatient hospital stay may be expected if axillary dissection is avoided. Node-negative patients would avoid the potential morbidity of formal axillary clearance. The two previously reported large studies on sentinel node localization in breast cancer have shown similar encouraging results, using two different techniques[13,15]. The techniques may be complementary; lymphatic mapping using a combination of both blue dye and a radiolabelled colloid may be an improvement.

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Oesophageal cancer staging using endoscopic ultrasonography

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Background Despite encouraging results from Europe and the USA, endoscopic ultrasonography has yet to become established in the UK for imaging gastrointestinal lesions. The aim of this prospective study was to investigate the accuracy of endoscopic ultrasonography for local tumour (T) and lymph node (N) staging of oesophageal cancer.

Methods Endoscopic ultrasonography was performed in 50 consecutive patients with operable oesophageal cancer. Its accuracy for locoregional tumour staging was assessed and a detailed analysis of the distribution of ultrasonographically detected lymph nodes performed.

Results Endoscopic ultrasonography was highly accurate for both local tumour (92 per cent correct T stage prediction) and lymph node (86 per cent correct N stage prediction) staging compared with final histology. The procedure was also superior to open surgical staging performed by the surgeon; it had a tendency to overestimate malignant involvement of individual lymph nodes and had only limited ability to identify small benign lymph nodes, particularly in the abdomen.

Conclusion Endoscopic ultrasonography was reliable for both local tumour and lymph node staging of oesophageal cancer.

Oesophageal cancer is relatively uncommon in the Western world (UK 5·7 per 100 000; USA 3·2 per 100 000)[1,2]. The rising incidence of adenocarcinoma[2,3], however, and the generally poor prognosis of all oesophageal cancers[4,5] give this disease significant clinical impact. Overall 5-year survival rate is only 5–10 per cent[4,5]. Surgical attempts at cure carry significant morbidity, are costly and are appropriate in only a relatively small number of patients. The rational selection of patients should depend not only on fitness for surgery but also on accurate tumour staging to help identify patients in whom attempted cure is feasible[6].

Endoscopic ultrasonography has been in clinical use in Europe and the USA for over a decade[7,8]. It is valuable for high resolution imaging of gastrointestinal pathology[9,10] and its accuracy in local tumour (T) and lymph node (N) staging in oesophageal cancer is generally reported between 75 and 95 per cent for T stage[11–14] and between 70 and 90 per cent for N stage[15–17], although some series were small[18–20]. There have been no studies of its value for staging oesophageal cancer from the UK. The principal aim of this prospective study was to determine the accuracy of endoscopic ultrasonography for local tumour and lymph node staging in patients with oesophageal cancer compared with surgical and histological staging. A systematic evaluation of the distribution of ultrasonographically detected lymph nodes was also undertaken.

There is increasing evidence that the number and distribution of involved nodes might influence outcome. Metastasis to eight or more nodes[21] and, in particular, the involvement of multiple abdominal nodes[22,23] are both associated with decreased survival. The ability of endoscopic ultrasonography to distinguish between malignant and benign nodes based on morphological characteristics[24–26] makes it useful potentially for individual lymph node assessment.

Patients and methods

Fifty consecutive patients with oesophageal cancer diagnosed by endoscopic biopsy underwent endoscopic ultrasonography evaluation using an Olympus (Olympus Optical, Tokyo, Japan) EUS-M20 radial scanning echo endoscope. None had evidence of haematogenous spread based on a combination of computed tomography (CT) of chest and abdomen, transcutaneous abdominal ultrasonography and plain chest radiograph. All patients were considered fit for surgical resection. Forty-seven patients underwent oesophagectomy within 6 weeks of endoscopic ultrasonography and the remaining three after 8, 9 and 12 weeks. Endoscopic ultrasonography scanning was done on an outpatient basis in a dedicated endoscopy unit. Staging data were gathered from three sources: endoscopic ultrasonography, the surgeon who performed the resection and final histology using a standard examination. Surgical staging data were obtained from direct observation by the principal surgeon according to a standard protocol.

Based on previous experience[16] and trial dissections of individuals scanned at this centre, tumours with contiguous organ invasion (T_4) did not receive surgery. It was considered inappropriate to subject such patients to the extended lymphadenectomy necessary to determine the distribution of nodal involvement.

Endoscopic ultrasonographic T staging was performed by observing directly the depth of penetration of the tumour through the component layers of the oesophageal wall seen on endoscopic ultrasonography as a series of alternating hypoechoic rings[27–30]. T_1 tumours involved the mucosa or submucosa but not the muscularis propria, T_2 tumours involved the muscularis propria but not the adventitia, T_3 tumours were full thickness involving adventitial tissues and T_4 tumours involved adjacent organs by contiguous invasion. Lymph nodes were designated benign or malignant by endoscopic ultrasonography according to the presence or absence of a number of morphological characteristics summarized in *Table 1*. Technical difficulties with the ultrasonography scanner resulted in the exclusion of one patient from lymph node analysis.

Results

Twenty-nine (58 per cent) patients had adenocarcinoma and 21 (42 per cent) had squamous cell carcinoma. Eight

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Table 1 Lymph node evaluation using endoscopic ultrasonography

Criterion	Malignant	Benign
Size	Large	Small
Shape	Round	Elliptical or flat
Echo density	Echo poor	Echo dense
Heterogeneity	Homogenous	Heterogeneous
Grouping	Solitary	Clusters
Borders	Regular	Irregular

Table 3 Endoscopic ultrasonography *versus* surgical staging: evaluation of N staging accuracy

$n = 49$	N_0	N_1	Sensitivity	Specificity*	PPV*	NPV*	κ
EUS-N	8	41	97	54	0·85	0·88	0·61
Histology-N	13	36	—	—	—	—	—
Surgical-N	17	32	81	75	0·91	0·56	0·47

Lymph node stage designation as node positive (N_1) or node negative (N_0). PPV, positive predictive value; NPV, negative predictive value; EUS, endoscopic ultrasonography. *Calculated against histological stage[31]

Table 2 Endoscopic ultrasonography *versus* surgical staging: evaluation of T staging accuracy

$n = 50$	T_1	T_2	T_3	T_4	Sensitivity*	Specificity*	PPV*	NPV*	κ*
EUS-T	1	8	40	1	97	73	0·93	0·89	0·72
Histology-T stage	1	10	38	1	—	—	—	—	—
Surgical-T stage	1	17	31	1	79	91	0·97	0·56	0·59

Tumour stage designation as full (T_3 or T_4) or partial (T_1 or T_2) thickness. PPV, positive predictive value; NPV, negative predictive value; EUS, endoscopic ultrasonography. *Calculated against histological stage[31]

tumours were in the middle-third and 42 in the distal-third of the oesophagus. Eleven of the 50 tumours (22 per cent) had caused sufficient luminal stenosis to prevent passage of the echo endoscope beyond the lesion. In these patients endoscopic ultrasonography was incomplete because imaging distal to the tumour was impossible.

Local tumour staging

Table 2 shows close approximation between endoscopic ultrasonography and histology for local tumour staging. Surgical staging was less reliable with a tendency to underestimate the extent of local spread. Comparison of endoscopic ultrasonography with histological staging for individual patients revealed four staging errors (8 per cent). Three were a result of overstaging, all T_2 tumours incorrectly designated T_3 by endoscopic ultrasonography. A single T_3 lesion was understaged as T_2 by endoscopic ultrasonography. Nine (18 per cent) surgical staging errors were made compared with final histology. Eight were understaging errors, all T_3 tumours incorrectly designated T_2 by surgical staging, and one was overstaging of a T_2 tumour as surgical-T_3.

Overall sensitivity and specificity values have been calculated for T stage by distinguishing between full- and partial-thickness tumours (*Table 2*). Some 97 per cent of full-thickness tumours (T_3 or T_4) were detected accurately by endoscopic ultrasonography with high sensitivity and positive predictive value. Surgical staging was inferior to endoscopic ultrasonography in the detection of full-thickness tumours.

Lymph node stage

Forty-one patients were designated N_1 by endoscopic ultrasonography and eight were N_0. The median number of nodes detected per patient (not categorized as either malignant or benign) was four (interquartile range 3–6).

Seven (14 per cent) lymph node staging errors were made by endoscopic ultrasonography; six were overstaging errors. Ten (20 per cent) staging errors occurred with surgical staging, of which seven were understaging and three were overstaging errors (*Table 3*). Sensitivity and specificity values for both endoscopic ultrasonography and surgical lymph node staging compared with histological staging are also shown in *Table 3*.

Table 4 Total lymph nodes detected by endoscopic ultrasonography and histology

	EUS	Histology
Nodes		
All	236	438
Malignant	113	123
Benign	123	315
Malignant : benign ratio	1 : 1·09	1 : 2·56

EUS, endoscopic ultrasonography

Table 5 Distribution of mediastinal and abdominal lymph nodes

	EUS ($n = 49$)	Histology ($n = 49$)	Histology (patients without oesophageal obstruction ($n = 38$)
Nodes			
Mediastinal	197	204	141
Abdominal	39	234	173
Mediastinal : abdominal ratio	5 : 1	0·87 : 1	0·81 : 1

EUS, endoscopic ultrasonography

Endoscopic lymph node detection

Table 4 compares the predicted malignant involvement of lymph nodes detected by endoscopic ultrasonography with all malignant nodes detected by histology. The malignant : benign ratio of the nodes detected by endoscopic ultrasonography was almost 1 : 1, although more lymph nodes in total were detected by histology than endoscopic ultrasonography at a ratio of almost 2 : 1. The total numbers of malignant nodes detected by each modality were virtually identical, most of the additional nodes detected histologically were benign.

There was good agreement between the total number of mediastinal nodes detected by endoscopic ultrasonography and histology, but far fewer abdominal nodes were detected by ultrasonography than by histology (*Table 5*). Even after exclusion of the 11 patients with obstructing oesophageal lesions (in whom ultrasonic evaluation of abdominal nodes was not possible) there was still a large difference between the number of abdominal nodes detected by ultrasonography and histology. The former detected five times as many mediastinal nodes as abdominal nodes, whereas with histological examination the ratio was nearer 1:1 (*Table 5*). The majority of nodes missed by endoscopic ultrasonography were benign and lying below the diaphragm. Almost equal numbers of malignant nodes were detected by ultrasonography and histology (*Table 3*).

Lymph nodes detected above and below the diaphragm were divided into malignant and benign groups and the data compared. In the mediastinum endoscopic ultrasonography identified virtually the same total number of lymph nodes as final histology (197 *versus* 204), but ultrasonography overestimated the malignant status of individual nodes (93 of 197 for endoscopic ultrasonography *versus* 64 of 204 for histology). A different situation existed with abdominal nodes (*Table 5*). Endoscopic ultrasonography detected very few abdominal lymph nodes in total compared with histology (39 *versus* 173 for the 38 patients with a patent oesophagus). Furthermore, far fewer nodes were identified as malignant by ultrasonography (20 of 39) compared with histology (36 of 173).

The detection rates of neoplastic nodes by endoscopic ultrasonography and histology for each patient were evaluated to determine agreement, excluding the 11 patients in whom malignant oesophageal obstruction prevented examination of abdominal nodes by endoscopic ultrasonography.

Endoscopic ultrasonography tended to overestimate lymph node involvement (*Fig. 1*), although where overestimation occurred, it was usually by a single lymph node at most. Significant discrepancies in lymph node counts (over four) between endoscopic ultrasonography and histology occurred in only three patients. Assessing these patients individually, in one, overestimation of the malignant involvement of detected nodes was the source of error, whereas in the other two, the discrepancy was due to failure of endoscopic ultrasonography to detect large numbers of involved abdominal lymph nodes. In the remaining 35 patients, however, agreement was much closer between the two techniques. Exact agreement between the malignant lymph node counts occurred in only 16, although a match within a single lymph node was achieved in 30 patients.

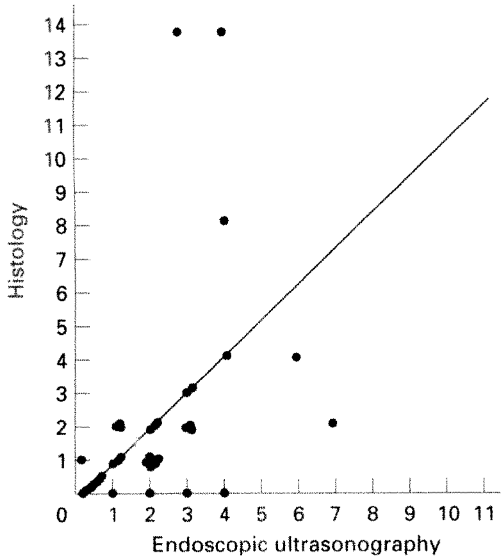

Fig. 1 Agreement for malignant node detection: endoscopic ultrasonography *versus* histology (malignant nodes per patient)

Discussion

This study has shown that endoscopic ultrasonography is highly accurate for the prediction of local tumour infiltration when compared with histology[17,32,33], and superior to open surgical assessment. It is not as reliable for lymph node staging, particularly in node-negative patients, but is still superior to surgical assessment of lymph node stage.

The reliability of endoscopic ultrasonography for local tumour staging has important clinical implications[34]. It aids the preoperative identification of patients with a tumour that has not yet penetrated the full thickness of the oesophageal wall. For resectable tumours the distinction between partial- and full-thickness penetration is an important determinant of long-term survival[35] and local recurrence[36]. Endoscopic ultrasonography can therefore identify patients in whom a surgical cure may be possible, if they are also lymph node negative. Patients with full-thickness tumours are less likely to be cured by surgery alone but, with the continuing development of chemoradiotherapy techniques, endoscopic ultrasonography may help identify patients who could benefit from neoadjuvant therapy. The preoperative identification of individuals with contiguous organ invasion, which renders tumours irresectable, rationalizes the use of resources and prevents unnecessary surgery[16,37]. There is a valid argument for the selection of therapeutic regimens other than radical surgery with its attendant morbidity and mortality[5,38], in patients with little or no prospect of cure.

Accurate lymph node evaluation is important because node stage also affects prognosis[35]. Only 50 per cent of patients with lymph node metastases will be alive 2 years after resection, and just 15 per cent survive more than 5 years[39]. The actual number of involved lymph nodes might also be important. Recent evidence suggests that the presence of a large (more than seven) number of involved nodes, and in particular multiple abdominal nodes, is associated with reduced survival[21,22,40]. Consequently, a subgroup of patients might once again be identifiable who might benefit from non-surgical therapy. Oesophagectomy alone is appropriate treatment for patients with partial-thickness, lymph node-negative tumours.

This study has identified two important sources of error for lymph node evaluation by endoscopic ultrasonography. First, some benign lymph nodes detected in the mediastinum were incorrectly designated malignant. The identification of nodes by endoscopic ultrasonography does not necessarily imply nodal metastasis. Possible sources of error include classification of large nodes as malignant rather than reactive, and errors in the interpretation of ultrasonic lymph node characteristics. The development of ultrasonographically guided fine-needle aspiration cytology could enhance staging accuracy.

The second limitation of endoscopic ultrasonography is its failure to detect many of the regional nodes in the abdominal cavity. The majority of nodes that were 'missed' by endoscopic ultrasonography were small and benign[41], although many malignant abdominal nodes were also missed. Small, malignant abdominal nodes, however, rarely occurred in isolation, so this had little impact on overall staging accuracy.

The overall impact of these sources of error is quite small. Lymph node staging was correct in 85 per cent of all patients, and the individual identification of malignant nodes matched final histology to within a single node in 80 per cent of cases.

In this study, overall T and N staging accuracy was not greatly affected by obstructing oesophageal tumours. Obstructing tumours were almost always T_3 N_1, detectable on limited mediastinal scanning alone. Important prognostic information about coeliac node involvement is, however, not available if abdominal endoscopic ultrasonography cannot be performed. Endoscopic ultrasonography from within the stomach is technically more demanding than from within the oesophagus. Not all lymph nodes present are within scanning range. The failure of endoscopic ultrasonography to detect every single lymph node present might, however, be of little clinical importance, provided that it detects malignant nodes reliably and only fails to detect mainly benign nodes.

In future, node staging is worthy of further study with endoscopic ultrasonography although a number of technical advances will be needed to improve its accuracy. The availability of scanners using higher frequency ultrasonography than 12 MHz will increase image resolution. As experience increases in the more technically difficult technique of gastric endoscopic ultrasonography, the ability to detect lesser curve and coeliac nodes may improve. The additional preoperative staging data provided by endoscopic ultrasonography and its impact on patient selection and long-term outcome will require careful assessment.

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Influence of luminal obstruction on oesophageal cancer staging using endoscopic ultrasonography

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Background Endoscopic ultrasonography is technically limited in patients with obstructing oesophageal cancers if the endoscope cannot pass beyond the lesion. This problem may be overcome by preliminary endoscopic tumour dilatation, or by the use of narrower calibre 'blind' endoscopic ultrasonographic telescopes or fine-bore endoscopic ultrasonographic miniprobes. These alternatives are either potentially hazardous or time consuming and expensive. The aim of this prospective study was to determine the effect of oesophageal obstruction on the locoregional staging accuracy of endoscopic ultrasonography for oesophageal cancer.

Methods Some 50 patients with oesophageal cancer underwent staging with endoscopic ultrasonography before oesophagectomy and the T and N stage determined by endoscopic ultrasonography was compared with final histology. In 11 cases of luminal obstruction no attempt was made to overcome the blockage and a limited mediastinal scan alone was performed.

Results Malignant obstruction of the oesophagus did not greatly reduce the staging accuracy of endoscopic ultrasonography. It correctly assessed local infiltration in all patients with obstruction, and correctly predicted nodal stage in nine of 11 patients.

Conclusion Tumours large enough to cause luminal obstruction are nearly all full thickness (T_3), and frequently have mediastinal lymph node metastases (N_1) at the time of examination. This can usually be detected from limited endoscopic ultrasonography within the mediastinum.

Endoscopic ultrasonography is an imaging technique which combines high-frequency ultrasound and conventional endoscopy in a single instrument. It provides high-resolution images of the gastrointestinal tract wall and adjacent structures[1,2]. There is mounting evidence to show that, in patients with oesophageal cancer, endoscopic ultrasonography is the most accurate preoperative local tumour and lymph node staging investigation[3–5]. It is the only imaging modality that can demonstrate the precise depth of mural invasion[6] and can detect regional and more distant lymph nodes down to just a few millimetres in diameter[7]. It also demonstrates their internal structure, allowing prediction of individual lymph node status, based on sonographic characteristics, rather than size alone[8,9].

One commonly reported limitation of endoscopic ultrasonography is that a significant proportion of tumours obstruct the oesophageal lumen[10,11], preventing assessment of distal parts of the primary tumour, distal mediastinal structures, the stomach and the abdominal lymph nodes. One possible solution to this problem is endoscopic tumour dilatation before endoscopic ultrasonography thereby permitting a full staging examination[12]. The use of fine-bore ultrasound miniprobes has been advocated as a means of overcoming malignant obstruction[13], but the equipment is expensive and the instruments cannot be steered. More recently, relatively narrow, steerable, but optically blind ultrasonography endoscopes have been developed to help traverse some stenotic lesions. Time consuming or potentially dangerous procedures such as these may not be justified if the staging accuracy of endoscopic ultrasonography is not significantly reduced in such cases of tumour obstruction.

The aim of this study was to compare the staging accuracy of endoscopic ultrasonography with final histological stage using the tumour node metastasis (TNM)[14] staging system for obstructing and non-obstructing oesophageal cancers in patients with operable tumours undergoing oesophagectomy.

Patients and methods

Fifty consecutive patients with potentially resectable oesophageal cancer underwent preoperative tumour staging with endoscopic ultrasonography using a 13-mm diameter Olympus EU-M20 radial scanning echo endoscope (Olympus, Tokyo, Japan). All patients were considered fit for surgery, with no evidence of haematogenous metastasis on computed tomography. Predictions of the local tumour stage (T) and regional lymph node stage (N) using the TNM system were made using endoscopic ultrasonography and compared with the final histological stage, following oesophagectomy. The endoscopic ultrasonography stage was not used to influence the decision to perform resection, which was carried out in all 50 patients. The proportion of patients in whom only a limited (proximal) endoscopic ultrasonographic investigation could be performed because of malignant obstruction of the oesophagus was determined and the staging accuracy of endoscopic ultrasonography for patients with obstructing and non-obstructing lesions was compared with the final histological stage. When assessing lymph node involvement, data from a single patient were excluded because of a technical fault with the echo endoscope during scanning.

Results

Passage of the echo endoscope was prevented by malignant obstruction in 11 (22 per cent) of 50 patients. In these cases examination was restricted to the upper part of the primary tumour and mediastinal structures

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proximal to the obstruction. In the other 39 patients a full staging investigation was performed, including distal assessment of the stomach, and coeliac axis, lesser and greater curve lymph nodes.

Endoscopic ultrasonography predicted full-thickness wall penetration, but without contiguous organ invasion (T_3) in 41 of the 50 tumours and malignant lymph node involvement in 41 of 49 patients. For comparison, on final histological examination 39 tumours were found to be full thickness (T_3 lesions) and 36 were lymph node positive (N_1).

Of the 11 tumours that obstructed the oesophageal lumen all were T_3 histologically. Despite the limited endoscopic ultrasonographic examination performed in these patients, endoscopic ultrasonography correctly identified all tumours as full-thickness lesions (T_3) (*Table 1*).

Endoscopic ultrasonography designated all 11 tumours as N_1 lesions, even though nodes could only be visualized in the mediastinum proximal to the tumours (median 3 (range 1–5) malignant nodes per patient). Histological N staging compared favourably with endoscopic ultrasonography results; nine of the 11 patients were lymph node positive on histological examination (*Table 1*) (median 2 (range 0–5) malignant nodes per patient). Accurate T and N staging information was therefore readily obtainable by endoscopic ultrasonography in every patient for local tumour stage and in nine of 11 patients for regional node stage, without scanning distal to the tumour.

Abdominal lymph nodes cannot be detected if the echo endoscope does not pass distal to the primary tumour and this may be clinically important. A total of 18 malignant abdominal nodes were detected by histological examination of the resected tumour specimens in six of the 11 patients with obstruction (range 1–5 malignant nodes per patient). On final histology five were designated lesser curve nodes, eight left gastric nodes, two greater curve nodes and three were unspecified. The maximum recorded size was 1·8 cm and the minimum 0·5 cm. In all six of these patients, however, histologically malignant mediastinal nodes were also present (N_1) and in each patient this feature was detected successfully by a limited (i.e. proximal mediastinal) endoscopic ultrasonographic scan alone.

For the 50 patients there were only four T staging errors made by endoscopic ultrasonography (sensitivity 97 per cent, specificity 73 per cent, positive predictive value (PPV) 0·93, negative predictive value (NPV) 0·89). Overstaging occurred three times and understaging once (*Table 2*). A further seven lymph node staging errors were made by endoscopic ultrasonography (sensitivity 97 per cent, specificity 54 per cent, PPV 0·85, NPV 0·88). Lymph node status was overstaged by endoscopic ultrasonography six times and understaged once (*Table 2*). All four local tumour staging errors occurred in patients whose oesophageal lumen was patent and in whom a complete staging examination had therefore been performed. Only two of seven lymph node staging errors occurred in patients with malignant obstruction.

Table 1 T and N staging in 11 obstructing tumours by endoscopic ultrasonography *versus* histology

	EUS	Histology
Full thickness (T_3)	11	11
Malignant lymph nodes (N_1)	11	9

EUS, endoscopic ultrasonography

Table 2 Frequency and type of T and N staging errors using endoscopic ultrasonography

Successful investigations	Staging errors	Overstaged	Understaged
T ($n = 50$)	4 (8)	3	1
N ($n = 49$)	7 (14)	6	1

Values in parentheses are percentages

Discussion

Malignant oesophageal obstruction leading to incomplete endoscopic ultrasonographic examination occurred in 22 per cent of patients ($n = 11$), a similar rate to that seen in other series[10,11,15]. Ten impassable lesions were encountered in the first 25 patients and only one in the next 25 suggesting that moderately tight stenoses can be overcome with experience.

Local tumour penetration was assessed correctly for all obstructing tumours as endoscopic ultrasonographic T_3 lesions, confirmed by final histology. Lymph node involvement was correctly assessed in nine of the 11 obstructing tumours. The presence of malignant oesophageal obstruction therefore made little difference to the T and N staging accuracy of endoscopic ultrasonography for oesophageal tumours. In the complete series of 50 patients, most of the staging errors made by endoscopic ultrasonography occurred in patients in whom there was no oesophageal obstruction and in whom a full staging examination had therefore been carried out.

There was a clear relationship between luminal obstruction and the local tumour and lymph node stage. Oesophageal tumours that were advanced enough to obstruct the passage of a 13-mm diameter echo endoscope tended to be locally advanced (T_3)[15] with regional lymph node metastases already present at the time of examination[16,17]. Even limited endoscopic ultrasonography at the level of or proximal to the obstructing tumour revealed both of these key features in most patients.

In this study the T and N stage was usually assessed correctly by endoscopic ultrasonography in patients with obstructing lesions. It is true, however, that not every aspect of the tumour anatomy will necessarily be revealed by such limited scanning. Potentially important prognostic information about coeliac node involvement, in particular, is not available. This is significant because spread to coeliac and cervical lymph nodes is currently classified as distant (M_1) rather than regional (N_1) spread.

Failure to pass every tumour may be more important in upper and middle third tumours where local airway infiltration or fixation to great vessels is more likely, and where understaging a T_4 tumour could lead to unnecessary surgery for unresectable disease. It is conceivable that only the distal portion of an obstructing tumour, beyond the reach of endoscopic ultrasonography, may be T_4 while the proximal portion is staged as T_3. This situation is less problematic with distal third tumours, as aortic, pericardial and pulmonary involvement are not common and can still usually be dealt with by excision. Although all the patients in this study had potentially resectable tumours, other studies have shown endoscopic ultrasonography to be generally reliable for detecting contiguous invasion (T_4 lesions)[18,19].

For the purposes of locoregional tumour staging alone, it is therefore difficult to justify the use of potentially hazardous procedures, such as endoscopic tumour dilatation to facilitate more distal passage of the echo endoscope, merely to complete the scan. Tumour dilatation may be necessary for nutritional purposes, in which case a complete scan may then be performed, although the only likely advantage would be the identification of further gastric and coeliac lymph node metastases, in patients who also have mediastinal spread. It is similarly difficult to justify the expense of fine-bore, non-steerable, high-frequency miniprobes[5,13] to negotiate tight strictures, when this may add little to overall staging accuracy. The development of narrower diameter, but steerable echo endoscopes ('oesophagoprobes') may be a useful compromise between bulky, conventional echo endoscopes and non-steerable miniprobes, and should render fewer tumours truly impassable.

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Comprehensive 1-year cost analysis of open antireflux surgery in Nordic countries

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Background Antireflux surgery is a highly effective treatment option in patients with severe gastro-oesophageal reflux disease. However, because of the increasing pressure of cost containment within health care, cost aspects must also be added to the decision-making process.

Methods The aim of this analysis was to assess the total cost of open antireflux surgery during the first year after operation in 178 patients with chronic reflux, who were recruited into a controlled, prospective clinical trial. The study was carried out in 17 hospitals in the Nordic countries.

Results The cost of the operation represented more than 90 per cent of the direct medical costs which amounted to approximately US $5700. For a patient in the work force the indirect cost, i.e. loss of production, represented 47 per cent of the total cost, which was about US $10 800.

Conclusion The total cost profile of open antireflux surgery has now been established prospectively and can form a basis for future comparisons.

Antireflux surgery is highly effective in permanently controlling symptoms with few failures, the majority of which seem to occur during the early postoperative period[1–4]. However, modern medical therapy is also effective in the long term[5,6]. Therefore, in the choice between different therapeutic strategies in chronic gastro-oesophageal reflux disease (GORD), different aspects, which are fundamentally different in character, have to be added to the decision-making process. One important factor is the cost. Unfortunately, very few controlled prospective clinical data are available to allow proper definition and characterization of the true costs of different therapies for chronic diseases in general and GORD in particular. The aim of this analysis was therefore to present the total costs for open antireflux surgery during the first year after operation when a variety of hospitals in the Nordic countries were engaged in the protocol. The main reason for focusing on this limited 1-year period was that the bulk of the cost associated with the surgical therapeutic option occurs during this period.

Patients and methods

Eligible for inclusion in the study were patients with chronic reflux symptoms and documented oesophagitis at endoscopy. These patients were initially given omeprazole either 20 or 40 mg daily for up to 4 months to control symptoms and to heal the oesophagitis. One hundred and fifty-four patients were initially randomized to have antireflux surgery within 3 months of the randomization, but ten of these patients subsequently refused operation. Among the patients recruited originally, 34 had an incomplete symptom response and/or endoscopic healing when taking omeprazole 40 mg daily, whereupon they were offered antireflux surgery according to the protocol and ultimately accepted an operation. Therefore, in total 178 patients, with a mean age of 50 (18–74) years, were operated on, of whom 75·3 per cent were men (*Table 1*). There were no important differences in the demographic profile of those initially randomized to surgery and those having an incomplete symptomatic response to omeprazole (*Table 1*). The majority of patients had a history of reflux disease lasting more than 5 years. At preoperative endoscopy 115 patients had grade 2 oesophagitis, 41 grade 3 disease and 21 grade 4 disease as assessed according to a predefined protocol[7].

The participating centres and the investigators responsible have been presented elsewhere[8]. All operations were carried out under general anaesthesia through an upper midline incision; 121 patients had a 360° total fundic wrap and 53 had a semi-fundoplication according to Toupet or slight modification of this partial fundoplication[9–11]. Five patients had a posterior gastroplexy according to Hill combined with a highly selective vagotomy[12].

The mean operating time was 103 (range 40–240) min. The mean hospital stay was 7·3 days. The postoperative course and complication rates have been described in detail elsewhere[8]; five patients (2·8 per cent) required splenectomy. During the

Table 1 Demographic data of patients randomized to antireflux surgery after complete response to or after a partial response to omeprazole

	Randomized ($n = 144$)	Partial response ($n = 34$)
Sex ratio (M:F)	110:34	24:10
Smokers (%)	23	53
Alcohol (> 3 drinks/week) (%)	28	18
GORD duration (years)		
1–2	12	1
3–5	33	8
6–10	43	8
11–20	41	12
21–48	15	5

GORD, gastro-oesophageal reflux disease

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immediate postoperative period, six patients experienced complications which required operative reintervention. Forty-six patients had one postoperative adverse event, only three had three or more complications. During the first postoperative year, 14 patients (seven operated) were diagnosed to have an incisional hernia and one patient had a reoperation for recurrent reflux. During the year after operation, moderate to severe reflux symptoms were reported by 19 patients (10·7 per cent) at least once during the first 3 months. Persistent reflux symptoms, requiring omeprazole therapy, were noted in ten patients (5·6 per cent).

Assessment and calculation of costs

A prospective protocol was used to register all costs which appeared during the management of the patients during the first year of the study.When there was no observation under a specific item, no cost was registered. Both direct and indirect costs were considered. The direct medical costs included antireflux surgery, days in hospital, visits to a doctor, visits to a nurse, endoscopy, medical therapy in case of relapse, reoperation or other surgical procedures. Additional direct costs were those associated with travelling. Indirect costs were assessed in the form of loss of production due to absence from work in association with the operation and hospital visits.

The unit cost of an operation, reoperation, hernia surgery and endoscopy are from internal, prospective assessments done at Sahlgrenska University Hospital, Gothenburg, Sweden. The cost of an operation included the so-called hotel cost (days in hospital). The cost of an outpatient visit to a doctor was set equal to the mean cost of an outpatient visit to a Swedish county hospital (Landstingsförbundet, 1995). The cost of a visit to a nurse was set at 25 per cent of that to a doctor. The cost per 20 mg capsule of omeprazole was derived from the retail price of a package of 28 capsules.

The cost per minute of travel by private car was arrived at by creating a relationship between time and distance, based on 559 eligible questionnaires, and an assumed cost of 25 Swedish crowns (SEK) per 10 km. With regard to public transport and taxi the questionnaire included a question on the cost. Hence, it was possible to establish a direct relationship between time and cost. Based on 144 questionnaires filled in by Swedish patients, the cost of travelling by public transport and taxi was 0·41 and 7·60 SEK per min respectively. Other modes of transport were assumed to result in no cost.

The cost per hour of absence from work equalled the cost per hour for an industrial worker in Sweden during the actual time period. In May 1995 this total cost was 153·50 SEK (US $19·4).

Hospital visits and endoscopies not likely to occur in clinical practice were excluded from the main analysis (protocol-driven visits and endoscopies occurring despite the fact that the patient was asymptomatic). However, for comparison, costs were also calculated with all visits and endoscopies included.

It was assumed that trial-wide non-monetary quantities could be applied to each of the four participating Nordic countries, except the extent of sick leave, which was assumed to be country-specific. Monetary costs were calculated for Sweden, i.e. the non-monetary quantities were multiplied by appropriate Swedish unit costs and are expressed in US$ (in January 1998 1 US$ = 7·9 SEK).

The protocol and the case record forms were approved by the local ethics committees. Before entry into the trial all participants gave their written informed consent.

Results

Non-monetary quantities

The resource consumption in non-monetary terms is presented in *Table 2*. The mean hospital stay was 7·3 days. The 'as clinical practice' approach included 178 follow-up visits after surgery, nine extra visits and 16 protocol-driven visits necessitated by moderate or severe reflux symptoms and/or specific postoperative complaints. With the 'all visits included' approach, another 221 protocol-driven visits were included. The two approaches resulted in 1·1 and 2·9 visits to a doctor per patient respectively. In addition, there were 0·6 visits (109 in total) to a nurse. The number of endoscopies were accordingly calculated in two ways. The two approaches resulted in 0·2 and 1·0 endoscopies per patient respectively.

Table 2 Direct medical costs and indirect costs per patient submitted to antireflux surgery

Cost item	Quantity (mean no. per patient)	Cost per unit (US$)	Cost per patient (US$)
Direct medical costs			
Operation	1	5307	5307
Days in hospital	7·3	—*	
Outpatient visit (doctor)	1·1 (2·9)	165	181 (478)
Outpatient visit (nurse)	0·6	41	26
Endoscopy	0·2 (1·0)	141	28 (141)
Omeprazole	4·2	2·7	11
Reoperation	0·01	6267	63
Other surgical procedures	0·04	2555	102
Total direct medical cost			5718 (6126)
Indirect medical costs			
Absence from work			
Outpatient visit	0·6 (2·2) h	19·4	12 (43)
Endoscopy	0·5 (2·7) h	19·4	10 (52)
GORD symptoms and operation (per patient)	16·5 days	155	2557
Total indirect cost			2579 (2674)

Values in parentheses are corresponding figures, when all visits and endoscopies are included. *Included in cost of surgery. GORD, gastro-oesophageal reflux disease

As already noted, reflux relapse requiring omeprazole therapy was noted in ten patients. In addition, three patients received omeprazole therapy without having persistent reflux symptoms. Altogether these 13 patients consumed 746 20 mg capsules of omeprazole, a mean of 4·2 capsules per patient.

Reoperation was performed in one patient and repair of an incisional hernia in seven patients.

Based on 559 eligible questionnaires answered at outpatient visits the total travelling time per visit was estimated at 68 min. Private car and public transportation were the two most common modes of transportation.

In 260 of 628 eligible questionnaires the patient reported that he/she would have been working if not visiting the clinic. In 92 questionnaires the patient reported the assistance of a companion, 20 of whom reported absence from work due to the visit.

Data on sick leave in connection with operation were collected from the regional insurance office for patients at three centres in Sweden. Of 41 patients operated on at these centres sick leave was reported by 27 patients. On average, these patients had 47·2 days on sick leave. Assuming that approximately 70 per cent are days of absence from work, the number of days absence from work due to surgery was 33·0 per patient in the work force. Since the rate of employment among the patients in the study was 50 per cent, the average number of days absent from work was estimated to be 16·5 per patient.

Table 3 Cost per patient associated with antireflux surgery

	Cost (US$)		
	For a patient not in work	For a patient in work	Per patient (50% in work)
Direct medical cost	5718 (6126)	5718 (6126)	5718 (6126)
Transport cost	42 (78)	42 (78)	42 (78)
Indirect cost		5091 (5164)	2579 (2674)
Total cost	5760 (6204)	10 851 (11 368)	8339 (8878)

Values in parentheses are corresponding figures when all visits and endoscopies are included

Costs

The accumulated cost during the first year after and including antireflux surgery is given in *Table 2*. The travelling time reported in the questionnaires was multiplied by the mean number of trips necessitated by operation. Mean travel cost per patient was 42 US$. There were 0·7 visits to a doctor or nurse per patient (2·5 with 'all visits included' approach) and in 41·4 per cent of the visits the patient recorded absence from work due to the visit. In addition at 3·2 per cent of the visits the patient reported that he/she had a companion who was absent from work. Hence, the mean number of hours absence from work due to outpatient visits was 2 × 0·7 × 0·446 = 0·6 h (2 × 2·5 × 0·446 = 2·2 h for all visits including protocol-driven visits). Furthermore, 0·2 endoscopies were done per patient (1·0 with 'all visits included' approach) and it was assumed that each endoscopy resulted in a 6-h absence from work.

Given that half of the patients with GORD were working, the total average cost for antireflux surgery amounted to 8339 US$, when based on clinical practice and to 8878 US$, when all study visits and endoscopies were included. When based on clinical practice, the direct medical cost constituted close to 70 per cent of the total cost, and the costs of operation represented more than 90 per cent of the direct medical cost (*Tables 2 and 3*). However, for a patient in the work force the total cost increased to 10 851 US$. For these patients the direct medical cost dropped to some 53 per cent of the total cost.

Discussion

The two most significant observations in this prospective assessment of the first year's cost of open antireflux surgery were that the cost of an operation represented more than 90 per cent of all direct medical costs, and that for a patient in the work force the indirect cost, i.e. loss of production, represented 47 per cent of the total cost.

The profound impact of the cost of the operative procedure has several important implications. First, it stresses the importance of accurate cost estimates. This is a significant problem in many health economic assessments. Charges and diagnosis-related group estimates are often used as approximations for the true cost. In this study the cumulative costs of antireflux surgery, assessed prospectively and in very detailed manner at one large hospital, were used to define the mean cost of the operations. Second, the cost of operation, and therefore the total cost, may vary substantially between different hospitals depending upon, among other things, local routines, organization and also the experience of the surgical team. Third, the limited weight of direct medical costs other than the cost of operation means that it may be possible to fairly correctly model the first year's direct medical cost given an accurate estimate of the cost of operation. However, this information can not of course be directly transferable to a model comparing surgery and medical treatment. Based on such a model it was concluded that operation appeared to be a cost-effective treatment option in patients with severe or refractory GORD compared with medical treatment[13,14] if the latter therapy lasted longer than approximately 4 years[15]. On the other hand, in another model it was found that surgery and medical treatment were equally cost-effective only if the follow-up time was extended to 9 years[16]. It is evident that prospective, controlled clinical trials, including assessments of costs, must be carried out to allow more comprehensive conclusions to be drawn. Finally, significant reductions in direct medical costs in the first year following operation can only be achieved by reducing the costs of operation including the hospital stay. The most promising surgical development is laparoscopic fundoplication[4,17], although the operating time is somewhat longer with this technique, the hospital stay is substantially reduced.

The number of days on sick leave in connection with surgery also deserves comment. First, the inclusion of indirect costs in a health economic analysis is controversial, since the range of costs included will depend very much on the true perspective of the analysis. The narrower the perspective, the narrower will be the relevant range of costs. However, all costs should in principle be considered, including the loss of production due to the disease or its treatment. On the other hand, there is disagreement about how absence from work should be validated[18,19]. In this analysis the common approach of attaching the total labour cost per hour to each hour of absence was used. It has been argued, however, that this approach may result in an overestimation of the true cost, especially when there is unemployment or when non-urgent work may be postponed[20]. A more general concern regarding the inclusion of indirect costs is that it favours intervention in diseases where most sufferers are among those in the work force. While this concern is valid and should be kept in mind when different diseases are compared[21], the authors believe it should not lead to the exclusion of indirect costs in individual analyses. Furthermore, the many days of sick leave observed in this study and the substantial impact of indirect costs on the total cost for a patient in the work force imply that modelling of the total cost, i.e. when assumptions are utilized to a large extent, may be very hazardous. Finally, the importance of sick leave points for the total cost profile highlights another area with potential for cost reduction. With laparoscopic fundoplication, sick leave is significantly reduced[4].

On the other hand, the present analysis has not considered so-called intangible costs, i.e. costs associated with pain, suffering and changes in social functioning[18,19]. These costs are generally very difficult to define in monetary terms. This issue is even more complicated in any analysis including surgical treatment, which is expected to result in future intangible benefits for the patient in the form of avoidance of relapses and other clinical consequences of uncontrolled GORD. Another methodological consideration in the assessment of intangible benefits between different treatment options is that these can at least partly be addressed by studying quality of life indices[22].

In conclusion, the present prospective, controlled multicentre trial has established a total cost profile of open antireflux surgery. The cost is profoundly influenced by the cost of the operative procedure with direct medical costs amounting to about 5700 US$. For half of the patients, who were in the work force, additional indirect costs of about 5000 US$ must be added resulting in a total cost of about 10 800 US$.

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Efficacy of anterior, posterior and total fundoplication in an experimental model

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Background This study examined the effect of different types of laparoscopic fundoplication on an incompetent lower oesophageal sphincter to test their effectiveness at preventing gastro-oesophageal reflux in the early postoperative period.

Methods An experimental porcine model was used. Initial oesophageal myotomy ensured an incompetent lower oesophageal sphincter with free reflux of 'intragastric fluid'. Anterior, posterior or total fundoplication was then performed laparoscopically in 15 laboratory pigs (five in each group). Fundoplication competence and efficacy were determined 2 weeks after laparoscopic antireflux surgery by inflating the stomach with liquid through a gastrostomy cannula. Some animals were also studied at 4 and 6 weeks. Lower oesophageal sphincter pressure was determined using a water-perfused oesophageal manometry catheter incorporating a Dent sleeve.

Results All three types of fundoplication produced similar increases in postoperative resting lower oesophageal sphincter pressure and restored adequate competence to the gastro-oesophageal junction.

Conclusion All three variants of laparoscopic fundoplication restore gastro-oesophageal competence in the early postoperative period.

The technique of Nissen's original total fundoplication has been modified progressively in order to reduce the likelihood of adverse outcomes following fundoplication for gastro-oesophageal reflux[1]. One variation has been the construction of a partial rather than a total fundoplication, with the fundus sutured either behind[2] or in front[3] of the intra-abdominal oesophagus. Which type of fundoplication is most effective and associated with the lowest incidence of adverse sequelae, however, continues to be debated in the surgical literature[3–5]. In some countries the recent advent of laparoscopic antireflux surgery has led to a surge in surgery for gastro-oesophageal reflux, with many centres now reporting the early results of large series[6–8]. The careful documentation of outcome from this new approach has provided an opportunity critically to reassess surgical techniques for the treatment of gastro-oesophageal reflux disease.

The Nissen procedure is associated with a small but important incidence of troublesome dysphagia[1], and some surgeons now prefer to perform a partial fundoplication for all patients. Early reports describe good short-term results with the partial approach, and they suggest that the rate of postoperative dysphagia may be lower[8,9]. However, long-term efficacy is less well documented. This study was undertaken using a porcine model to compare the adequacy of the antireflux mechanism produced by Nissen fundoplication against that produced by two partial fundoplication variants (anterior and posterior). All operations were performed laparoscopically.

The results of these three types of fundoplication undertaken in an *ex vivo* model have been reported previously[10]. Somewhat surprisingly, all three operations (i.e. anterior partial fundoplication, posterior partial fundoplication and total fundoplication) raised lower oesophageal sphincter pressure and acted effectively as an antireflux barrier. However, the artificial nature of the *ex vivo* model is obvious and this study was undertaken to examine the same operations *in vivo*.

Materials and methods

Fifteen domestic White pigs underwent laparoscopic antireflux surgery and postoperative evaluation. Following preliminary oesophageal myotomy, the pigs were randomly allocated to undergo either an anterior, posterior or total fundoplication (five in each group), with the operation performed by a surgeon experienced in laparoscopic antireflux surgery. Manometric evaluation was undertaken during the initial surgery, and subsequently 2 weeks after operation in all animals. Several animals also had 4- and 6-week postoperative studies. Fundoplication 'yield' studies were performed concurrently. Animals were treated in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes, and ethical approval for this study was granted by the Animal Ethics Committees of the University of Adelaide and the Institute of Medical and Veterinary Science, Adelaide, South Australia.

General operative procedure

After commencing general anaesthesia, access to the oesophageal lumen was achieved by the preliminary placement of an oesophagostomy cannula into the cervical oesophagus through a left neck incision. A purpose-built T-shaped plastic cannula 1 cm in diameter with arms 2 cm long was used, with the intra-oesophageal portion forming an open half circle when viewed in cross-section. This provided direct access to the oesophageal lumen, without obstructing the passage of swallowed liquids or solids.

Preliminary oesophageal manometry was performed to determine the baseline lower oesophageal sphincter pressure. An eight-lumen water-perfused manometry catheter incorporating a sleeve sensor (Dent Sleeve, Adelaide, South Australia) was passed through the oesophagostomy and then distally into the stomach. The position of the lower oesophageal sphincter was determined by gradually withdrawing the catheter and noting pressure changes as each sensor passed through the gastro-oesophageal junction. The catheter was then positioned so that

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the midpoint of the sleeve sensor was sited at the midpoint of the high-pressure zone. Resting lower oesophageal sphincter pressure was then measured over a 5-min period using the sleeve sensor. To eliminate the effect of intra-abdominal pressure, the basal end-expiration intragastric pressure was subtracted from that of the lower sphincter pressure to determine the resting lower oesophageal sphincter pressure.

Abdominal insufflation commenced following insertion of a Veress needle 2 cm above the umbilicus. Four laparoscopic ports were placed: 11-mm ports at the site of Veress needle insertion and in the left upper quadrant, and 5-mm ports in the epigastrium and left flank. A rigid curved instrument 4 mm in diameter was pushed through the abdominal wall of the right upper quadrant, and used to facilitate liver retraction, and to elevate the oesophagus following initial mobilization.

The oesophageal hiatus was dissected with laparoscopic scissors, and a distal oesophageal myotomy performed. This was extended approximately 1 cm on to the anterior wall of the stomach and 5 cm proximally, to divide the lower oesophageal sphincter completely. The pneumoperitoneum was then released and the lower oesophageal sphincter pressure was re-evaluated manometrically, to confirm complete sphincter ablation. This ensured that the subsequent fundoplication was responsible for any antireflux barrier tested during postoperative studies. The pneumoperitoneum was re-established and the hiatus was repaired posteriorly using one or two 2/0 polypropylene sutures.

Anterior fundoplication

An anterior fundoplication was fashioned by suturing the anteromedial gastric fundus to the right lateral wall of the distal oesophagus and concurrently to the posterior hiatal repair and right hiatal pillar with four or five interrupted sutures. The repair anchored a length of oesophagus within the abdomen, accentuated the angle of His, and fashioned a loose anterior 180° fundoplication.

Posterior fundoplication

To create a posterior fundoplication, the anteromedial fundal wall was drawn loosely behind the oesophagus and sutured to the anteromedial oesophageal wall with three sutures. A second row of three sutures secured the anterior fundus to the anterolateral oesophageal wall, fashioning a 270° posterior fundoplication, and leaving a strip of uncovered oesophagus 1 cm wide anteriorly, including the myotomized section.

Total fundoplication

A loose Nissen (circumferential) fundoplication 1·5–2 cm long was fashioned from the anterior wall of the fundus. It was secured by three sutures, which each included the oesophagus as well as the two pieces of stomach. An instrument was passed between the oesophagus and the fundoplication at the completion of the procedure to test that the fundoplication was not tight.

The pneumoperitoneum was then released and the lower oesophageal sphincter pressure was re-evaluated. The left upper quadrant port wound was extended to 4 cm in length, and the anterior gastric wall delivered. A flanged gastrostomy cannula 3 cm long and 1·5 cm in diameter was placed through an anterior gastrotomy and secured with a purse-string suture. This provided access to the gastric lumen for postoperative studies.

Postoperative studies

Postoperative studies were scheduled to take place at 2, 4 and 6 weeks after surgery. Sedation with ketamine was necessary to prevent discomfort from passage of the oesophageal manometry catheter and gastric distension. The manometric resting pressure generated by the fundoplication was determined using the sleeve sensor in the same fashion as in the preoperative studies. The catheter was then withdrawn and replaced by an 18-Fr nasogastric tube, with its tip sited 5 cm above the manometric high-pressure zone. A 24-Fr Foley catheter was passed into the gastric lumen through the gastrostomy cannula, and the catheter balloon was inflated to seal the gastrostomy. Competence of the gastro-oesphageal junction was assessed by infusing blue-coloured water into the gastric lumen. At the same time, the oesophageal tube was aspirated by a low-pressure suction device. Infusion continued until either blue water appeared in the oesophagostomy aspirate or the intragastric volume reached 2000 ml. The integrity of the gastro-oesophageal junction during progressive gastric distension was determined and the volume of intragastric fluid infused was recorded. No tube or measuring device crossed the gastro-oesophageal junction during these studies.

Statistical analysis

All data are presented as median (95 per cent confidence interval). Data sets were analysed using one-way analysis of variance to compare outcomes following anterior, posterior and total fundoplication.

Results

Fifteen domestic White pigs underwent the operation and subsequent postoperative studies. All pigs underwent studies 2 weeks after operation. Ten pigs were studied at the planned postoperative intervals during the 6-week study. The remaining five pigs were killed by barbiturate overdose between 2 and 5 weeks following surgery to avoid suffering from problems they developed from either the gastric or oesophageal cannulas. Three of these pigs underwent a Nissen fundoplication and two a posterior partial fundoplication. None of the problems encountered in these five animals was associated with the type of fundoplication performed. No difficulties with the intake of either oral fluids or solids were encountered in any animal.

The duration of surgery and the associated intraoperative studies was similar for each fundoplication variant (all median 120 min; $P = 0{\cdot}93$). The preoperative weights were similar for each group (anterior and Nissen fundoplication groups 20 kg, posterior fundoplication group 22 kg; $P = 0{\cdot}90$), as were the weights at the conclusion of the postoperative studies (anterior and Nissen 25 kg, posterior 27 kg; $P = 0{\cdot}65$). All animals resumed oral liquid and solid intake at similar time intervals, irrespective of the fundoplication type, with liquids tolerated within 24 h of surgery and solids resumed a day later.

The pressures measured manometrically in the lower oesophageal sphincter region are summarized in *Table 1*.

Table 1 Lower oesophageal sphincter pressures

	Lower oesophageal sphincter pressure (mmHg)			
	Anterior	Posterior	Total (Nissen)	P*
Before operation	10 (− 3 to 30)	19 (6–33)	25 (1–54)	0·33
After myotomy	0 (0–0)	0 (0–0)	0 (0–0)	
After operation	10 (8–19)	14 (11–43)	14 (13–21)	0·067
Week 2	12 (9–13)	14 (4–16)	10 (4–16)	0·17
Final study	14 (9–20)	13 (7–22)	8 (2–15)	0·13

Values are median (95 per cent confidence interval). *One-way analysis of variance

Before oesophageal myotomy, a pressure ranging from 4 to 50 mmHg was measured at the gastro-oesophageal junction. In all instances, the subsequent distal oesophageal myotomy abolished this high-pressure zone. Subsequently, each fundoplication variant generated a significant rise in the intraluminal pressure measured at the gastro-oesophageal junction. The postfundoplication intraoperative measurement was lowest in the anterior fundoplication group, although this difference was not significant. The pressures recorded 2 weeks following surgery for each fundoplication variant were similar. Similarly, when the final lower oesophageal sphincter pressures recorded from each animal were analysed, the median pressures were similar, although a trend towards lower pressure following Nissen fundoplication was seen. Transient lower oesophageal sphincter relaxation events were not identified during any of the postoperative studies.

Two weeks after surgery, all of the anterior and posterior fundoplications and four of the five total fundoplications remained fully competent to the intragastric infusion of up to 2000 ml water. The Nissen fundoplication which yielded to gastric distension became incompetent following the infusion of 360 ml fluid. At 4 weeks all of the Nissen (two pigs) and posterior (three) fundoplications tested were fully competent. One of the five anterior fundoplications became incompetent following the infusion of 1300 ml. Two anterior and one posterior fundoplications yielded to the infusion of liquid 6 weeks after surgery, with the volumes infused at the point of fundoplication yield ranging from 1200 to 1800 ml.

Discussion

Both short- and long-term outcomes following Nissen fundoplication have been reported extensively in the era of open surgery and have confirmed the status of the Nissen fundoplication as the 'gold standard' for antireflux surgery. Long-term success rates of approximately 90 per cent can be expected following this procedure[1], although most reports following both open and laparoscopic surgery confirm a small but significant incidence of troublesome postoperative dysphagia[1,11,12].

Partial fundoplication has been proposed both for routine antireflux surgery and for patients with manometrically proven oesophageal dysmotility, with uncontrolled studies suggesting that the incidence of adverse outcomes may be reduced[3,13]. However, improvements in outcome have not been confirmed by randomized trials[4,12]. One uncontrolled study suggests that higher resting lower oesophageal sphincter pressures occur following Nissen fundoplication compared with partial fundoplication[13], and within the subset of patients undergoing Nissen fundoplication it has been postulated that adverse outcomes are more likely in patients with higher postoperative lower oesophageal sphincter pressures[1]. However, the fact that anterior partial fundoplication is associated with a lower resting lower oesophageal sphincter pressure, yet still controls reflux, suggests that reflux control is not dependent on the measured postoperative resting sphincter pressure alone[3].

The present study assessed the influence of different fundoplication types using a model in which the lower oesophageal sphincter was ablated completely before performing an antireflux procedure. The intraoperative lower oesophageal sphincter pressures measured immediately after construction of the fundoplication were greater following both total and posterior fundoplication than after anterior partial fundoplication, although the failure to reach significance may reflect the numbers involved. These results are similar to those reported in previous open surgical randomized trials in humans. These differences disappeared over the passage of several weeks.

A variety of mechanisms has been proposed to explain how antireflux surgery works. These include changes in various mechanical parameters acting at the gastro-oesophageal junction due to alterations in anatomy following fundoplication[14] and restoration of an adequate length of intra-abdominal oesophagus[15], as well as effects due to hormonal stimulation of the intrinsic gastric muscle within the portion of stomach used to construct the fundoplication[16], and acceleration of gastric emptying[17]. These effects may all lead to a reduction in the prevalence of transient lower oesophageal sphincter relaxations, a phenomenon that has been demonstrated following Nissen fundoplication[18].

Similar outcomes to those of the present study were reported in a previous study using a similar protocol in abattoir-sourced porcine viscera[10]. Resting lower oesophageal sphincter pressures in the *ex vivo* viscera model after various types of fundoplication varied from 11 to 13·5 mmHg and competence at the gastro-oesophageal junction was restored in most instances. The resting lower oesophageal sphincter pressures were of a similar magnitude to those measured in the present study, suggesting that fundoplication-induced manometric increases in the lower oesophageal sphincter zone may be due, at least in part, to passive mechanical factors. A similar *ex vivo* study has been reported by Richardson *et al.*[19]. Both of these studies suggest that physical factors associated with fundoplication may play as strong or even a stronger role in reflux prevention than alterations in the physiology of the area. When the stomach in *ex vivo* preparation is filled with fluid, the fundoplication becomes distended before the rest of the stomach[10], and this distension impinges directly on the lower oesophagus. This may also explain why such fundoplications seem to be effective when placed in the chest[20].

This study has confirmed that all three variants of laparoscopic fundoplication restore adequate competence to the gastro-oesphageal junction and result in similar increases in postoperative lower oesophageal sphincter pressure. This provides support for the uncontrolled clinical outcome studies following laparoscopic partial fundoplication which describe good results after each type of fundoplication, and for the previous randomized trials which demonstrated little difference between posterior partial fundoplication and total fundoplication[4,12]. As this study demonstrates that the laparoscopic anterior partial fundoplication provides an effective antireflux barrier, and uncontrolled studies suggest that it is clinically effective, the authors have commenced further assessment of this procedure within a prospective randomized trial of laparoscopic anterior partial fundoplication *versus* total fundoplication.

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Laparoscopy and laparoscopic ultrasonography in staging of oesophageal and cardial carcinoma

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Background The ideal method for staging tumours of the oesophagus and gastric cardia is not known. This paper was designed to assess the value of laparoscopy and laparoscopic ultrasonography in the staging of oesophageal and cardial carcinoma.

Methods From October 1993 to January 1996, 60 patients in whom no metastases were seen on gastroscopy, ultrasonography of the abdomen and supraclavicular region, helical computed tomography of the chest and abdomen or endosonography were scheduled for laparoscopy and laparoscopic ultrasonography.

Results Some 40 patients had carcinoma of the oesophagus, in one of whom liver metastases were found at laparoscopy and proven histologically. On laparoscopic ultrasonography metastases were found in four patients but were impossible to biopsy. These lymph node metastases were confirmed at exploratory laparotomy. Twenty patients had carcinoma of the gastric cardia; distant metastases were found in four at laparoscopy. On laparoscopic ultrasonography metastases were present in four further patients, all proven by biopsy.

Conclusion In this study laparoscopy was not an effective staging technique for oesophageal carcinoma. The inclusion of laparoscopic ultrasonography was of little benefit. A problem that was encountered was biopsy under laparoscopic guidance. In carcinoma of the gastric cardia, laparoscopy was more effective; adding laparoscopic ultrasonography doubled the number of patients seen to have metastatic disease.

In carcinoma of the oesophagus and cardia 60–80 per cent of patients are beyond cure at first presentation owing to widespread metastases or local irresectability of the tumour[1]. Thus, optimal preoperative staging is essential for selection of patients for curative resection. Despite the use of advanced imaging techniques such as endosonography and helical computed tomography (CT), metastatic spread or irresectability of the tumour is found in up to 20 per cent of patients during operation[2–8]. In particular, small liver metastases (less than 1 cm in diameter), lymph node metastases and peritoneal carcinomatosis are frequently encountered[3–8].

In recent years laparoscopy and laparoscopic ultrasonography have been used increasingly to stage abdominal malignancy. These techniques have proved to be highly successful in detecting liver, lymph node and peritoneal metastases in patients with pancreatic malignancy, with a sensitivity and specificity as high as 70–100 per cent[9–15].

The present study was performed to determine whether the combination of laparoscopy and laparoscopic ultrasonography is as effective in the staging of oesophageal and cardial carcinoma.

Patients and methods

From October 1993 to January 1996, 79 patients with biopsy-proven carcinoma of the oesophagus and/or cardia were referred for treatment. Distinction between tumours of the oesophagus and of the gastric cardia was made endoscopically by determining the hiatal impression and tumour bulk. The authors' service is a tertiary referral centre for patients with oesophageal and cardial carcinoma in the Netherlands. Thus, only patients considered potentially curable at other hospitals were referred. In this centre all patients are staged by means of the following techniques: gastroscopy, bronchoscopy in tumours of the upper and middle oesophagus, transcutaneous ultrasonography of the supraclavicular regions and abdomen (ATL HDI 3000; Bothell, Washington, DC, USA), contrast-enhanced helical CT of the chest and upper abdomen (100 ml Omnipaque 300, 2 ml/s; (Nycomed, Oslo, Norway); Envision CT injector (Medrad, Pittsburg, Pennsylvania, USA); collimation 8 mm, pitch 1·4, reconstruction increment 7 mm (Siemens, Erlangen, Germany)) and endosonography (GF-UM3, EU-M3; Olympus, Tokyo, Japan)[5–8]. Patients suspected of having distant metastases on the above-mentioned studies underwent biopsies to confirm metastases cytologically or histologically. Using these techniques about 70 per cent of patients referred to the authors' institution were finally subjected to surgery, 25 per cent were not operated on because of cytologically proven metastases and 5 per cent did not have surgery because of poor general condition[5]. In 19 cases distant metastases were proven and these patients were subsequently excluded from surgical treatment. Sixty patients had no metastases according to the above studies and were eligible for surgical resection. These patients were scheduled for staging by laparoscopy and laparoscopic ultrasonography.

Combined laparoscopy and laparoscopic ultrasonography was performed under general anaesthesia. A Hasson cannula was introduced in the subumbilical region. After pneumoperitoneum was obtained, a 10–12-mm cannula was inserted in the right and a 5-mm cannula in the left paramedian region under laparoscopic guidance. Laparoscopic staging included inspection of the peritoneum, greater omentum, diaphragm and liver capsule with a 0° telescope. Anatomical structures were manipulated with forceps inserted through the left paramedian port. If lesions suspect for metastases were found, a biopsy was taken to confirm the diagnosis histopathologically. In the absence

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of suspect lesions a laparoscopic ultrasound probe was inserted through the right paramedian port. The convex array, multifrequency 5–7·5-MHz probe with a semiflexible tip and a total length of 45 cm and diameter of 9 mm (type 8555; Brühl and Kjaer, Naerum, Denmark) was covered by a sterile sheath containing a small amount of gel. The ultrasound transducer was connected to a diagnostic ultrasound monitor (type 3555; Brühl and Kjaer). To optimize anatomical insight, laparoscopic and ultrasonographic images were displayed together on a Sony 14-inch video monitor. Ultrasonographic inspection included the liver, coeliac trunk, greater visceral vessels and primary tumour if located intra-abdominally. Ultrasonography was performed by a radiologist and imaging findings were discussed with the surgeon. Whenever possible a biopsy under ultrasonographic guidance was taken of lesions suspected of distant metastases.

If distant metastases could not be proven cytologically or histologically, patients were scheduled for transhiatal oesophageal resection irrespective of the laparoscopic and ultrasonographic findings. Patients with proven distant metastases were referred for palliative non-surgical treatment.

The effectiveness of laparoscopy and laparoscopic ultrasonography was defined as the additional number of patients in whom distant metastases were found with these techniques and the number in whom these findings had therapeutic consequences (e.g. cytologically or histologically proven distant metastases). In addition, the sensitivity and specificity of laparoscopy and laparoscopic ultrasonography were calculated.

Results

Sixty consecutive patients, 54 men and six women with a mean age of 61·7 (range 43–79) years, were included in the study. Forty patients had carcinoma of the oesophagus (squamous cell carcinoma, 15; adenocarcinoma, 25); 14 of the adenocarcinomas had developed in a Barrett's oesophagus. Adenocarcinoma of the gastric cardia was present in 20 patients.

Carcinoma of the oesophagus

In one of the 40 patients with oesophageal carcinoma liver metastases were found at laparoscopy. These metastases were proven histologically and the patient was referred for palliative non-surgical treatment.

On laparoscopic ultrasonography distant coeliac lymph node metastases were found in five patients. One of these five patients also had biopsy-proven liver metastases at laparoscopy. In the remaining four patients cytological or histological proof could not be obtained, because it was not possible to biopsy the suspect lymph nodes. These four patients underwent operation at which coeliac lymph node metastases were confirmed histologically. As a result of these findings the patients did not undergo resection, but were treated palliatively.

Two of 35 patients without distant metastases on laparoscopy with laparoscopic ultrasonography nevertheless had distant metastases at laparotomy (false-negative rate two (5 per cent) of 40). There were no false-positive findings (e.g. no enlarged lymph nodes on laparoscopic ultrasonography that did not contain metastases on histopathological study). The sensitivity of the procedure was 0·70, the specificity 1·00.

Carcinoma of the gastric cardia

At laparoscopy distant metastases were found in four of 20 patients: peritoneal metastases in three and omental metastases in one. In all cases metastases were confirmed histologically.

On laparoscopic ultrasonography distant metastases were found in four further patients: liver metastases in two and coeliac lymph node metastases in two. In all cases these metastases were confirmed histologically (*Table 1*).

All eight patients with histologically proven metastases were excluded from further surgical resection and were referred for palliative treatment

In one of 12 patients without metastases at laparoscopy and laparoscopic ultrasonography, distant metastases were nevertheless found during exploratory laparotomy (false-negative rate one (5 per cent) of 20). The sensitivity of the procedure was 0·88, the specificity 1·00.

For the total study population of 60 patients the sensitivity was 0·81 and the specificity 1·00.

Discussion

This study shows that laparoscopy is not an effective staging technique in patients with oesophageal carcinoma who have undergone substantial non-invasive radiological staging. Distant metastases are found in only a minority of cases. In addition it is of little benefit to include laparoscopic ultrasonography. With the combination of laparoscopy and laparoscopic ultrasonography, the number of patients in whom distant metastases were found was small.

In the authors' institution patients with oesophageal carcinoma undergo extensive radiological staging including transcutaneous ultrasonography of the abdomen and supraclavicular region, helical CT and endosonography before they undergo operation. It can be expected that the number of patients with metastases on laparoscopy and laparoscopic ultrasonography will be higher in cases where radiological staging is not so extensive[15].

A problem encountered in the present study was to prove metastases histologically when they were suspected on laparoscopic ultrasonography. Often it was difficult to

Table 1 Distant metastases as determined by conventional staging, laparoscopy and laparoscopic ultrasonography

	Adenocarcinoma ($n = 25$)	Squamous carcinoma cell ($n = 15$)	Total for oesophagus ($n = 40$)	Carcinoma of the cardia ($n = 20$)	Overall total ($n = 60$)
Conventional staging	0	0	0	0	0
Laparoscopy	1	0	1	4	5
Laparoscopic ultrasonography	2	2	4	4	8
Sensitivity	0·60	1·00	0·70	0·88	0·81
Specificity	1·00	1·00	1·00	1·00	1·00

biopsy lesions under ultrasonographic guidance, owing to the angle under which biopsies had to be performed and the enlarged distance between a lesion and the abdominal wall as a result of the insufflation of gas.

Although there were no false-positive findings on laparoscopic ultrasonography in this study, it has been shown previously that, because of the limited specificity of radiological modalities, lesions suspected for distant metastases on these studies should be confirmed histologically when therapeutic consequences are being considered[5].

In carcinoma of the gastric cardia laparoscopy was more effective. In four of 20 patients distant metastases were shown by this technique. By adding laparoscopic ultrasonography the number of patients in whom distant metastases were diagnosed was doubled. Strikingly, distant metastases could be proven more frequently in patients with carcinoma of the cardia than in those with oesophageal carcinoma. This is due mainly to the fact that peritoneal metastases accounted for three of eight of the distant metasases found in patients with carcinoma of the cardia in this study and technically it is a simple procedure to perform biopsy of peritoneal lesions under laparoscopic guidance. Performing biopsies of mobile lymph nodes that are more deeply located in patients with oesophageal carcinoma is technically more demanding.

In this study the sensitivity and specificity of laparoscopy and laparoscopic ultrasonography were acceptable for both oesophageal and cardial carcinoma. The results are consistent with those of laparoscopy for gastric carcinoma as reported by Burke *et al.*[16].

A disadvantage of the technique is that patients are submitted to an operative diagnostic procedure under general anaesthesia. It is the authors' opinion that this disadvantage counts for little compared with the number of patients in whom a laparotomy can be averted. In addition there is a certain risk of tumour spill as a result of the procedure, although there are no valid numbers in the literature to assess the extent of this risk. However, the true incidence of tumour spill has to be determined in a larger study. In the present study port site metastases did not occur during the brief follow-up period of 30 months.

The conclusion of this study is that diagnostic laparoscopy with laparoscopic ultrasonography is of little value in the staging of oesophageal carcinoma. This is due mainly to the small number of patients in whom distant metastases are found and the difficulty of confirming these lesions histologically. There is a role for laparoscopy with laparoscopic ultrasonography when staging patients with carcinoma of the gastric cardia, although this needs to be determined more fully in larger series. The additional value of ultrasonography compared with laparoscopic inspection is limited by ultrasonographically guided biopsy techniques; to improve the efficacy of this procedure further, better biopsy techniques should be developed.

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Controlled trial of preperitoneal local anaesthetic for reducing pain following laparoscopic hernia repair

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Background A prospective randomized trial was performed to determine whether local anaesthetic solutions injected into the preperitoneal space may provide additional pain relief following transabdominal preperitoneal laparoscopic hernia repair.

Methods One hundred patients undergoing transabdominal preperitoneal laparoscopic hernia repair were allocated randomly to receive (1) bupivacaine 1·5 mg/kg, (2) bupivacaine 1·5 mg/kg with 1 in 200 000 adrenaline, (3) bupivacaine 3 mg/kg or (4) saline instilled into the preperitoneal space at the end of the operation. An independent clinical assessor determined the level of pain using a visual analogue pain score and noted the parenteral and oral analgesia requirements at 4, 8, 12 and 24 h after operation.

Results At each of the time intervals, there was no significant difference between the groups for pain scores (at 24 h, $P = 0·71$) or the number of doses of either morphine (at 24 h, $P = 0·73$) or oral analgesia (at 24 h, $P = 0·89$). There was also no significant difference in the time to return to normal activity or work between the groups.

Conclusion This study suggests that instilling local anaesthetic into the preperitoneal space has no significant effect on postoperative pain relief requirement following laparoscopic hernia repair. Other methods of reducing postoperative pain should be sought that may facilitate day-case laparoscopic hernia surgery.

Evidence suggests that laparoscopic hernia repair is associated with a more rapid rehabilitation than conventional open herniorrhaphy[1,2]. Yet, unlike its open counterpart, laparoscopic hernia repair is not widely performed as a day-case procedure in the UK[3]. This could be related to the management of postoperative pain as a requirement for regular parenteral analgesia would prevent patients from meeting the criteria on day-case surgery[4,5].

The use of local anaesthetic in the port sites[6] or peritoneal cavity[7–10] following laparoscopic procedures is not proven to reduce analgesia requirement. In laparoscopic hernia repair instilling local anaesthetic into the confined preperitoneal space may represent a novel method of increasing the effect of the local anaesthetic[11]. If this resulted in a significant reduction in postoperative analgesia requirement more surgeons may be persuaded to perform day-case laparoscopic hernia surgery.

A prospective clinical trial was therefore performed to determine whether the instillation of local anaesthetic into the preperitoneal space following laparoscopic hernia repair reduces postoperative pain.

Patients and methods

One hundred patients (94 men, six women; median age 64 (range 27–83) years, undergoing transabdominal preperitoneal laparoscopic hernia repair were randomly allocated to receive (1) bupivacaine 0·25 per cent plain at a concentration of 1·5 mg/kg ($n = 25$); (2) bupivacaine 0·25 per cent (1·5 mg/kg) with 1 in 200 000 adrenaline ($n = 25$); (3) bupivacaine 0·5 per cent plain (3 mg/kg) ($n = 24$); or (4) saline 0·9 per cent ($n = 26$). Only the scrub nurse knew the randomization code, the anaesthetist, surgeon and clinical assessor all being blind as to the solution injected.

All preparations were injected at the end of the operation into the completely re-closed preperitoneal space via an introducer inserted through a 5-mm port. The port sites were not injected with local anaesthetic. The validity of the technique had been verified previously[11]. Postoperative pain relief consisted of intramuscular morphine 10 mg or a combination of paracetamol 500 mg and codeine phosphate 30 mg (Tylex; Schwarz, Chesham, UK) two tablets orally as required. Rectal non-steroidal preparations were not used.

All patients underwent operation in the morning, were observed overnight and reviewed the following morning. Total analgesia requirements at 4, 8, 12 and 24 h of operation were determined for each patient. An independent clinical assessor determined the overall level of pain at these time intervals using the McGill visual analogue pain scale[11]. An attempt was made to assess the different components of the pain as port site, preperitoneal space or visceral. Statistical comparisons between groups were performed using χ^2 analysis.

Results

There was no significant difference between the groups with respect to age, sex, American Society of Anesthesiologists grade, grade of surgeon performing the operation, length of operation or postoperative complications. Although patients complained more of visceral discomfort than pain in either the port or hernia sites, attempts at accurately assessing the site of the pain proved unsuccessful as most patients found it difficult to accurately localize the pain in the early postoperative phase.

The median (range) doses of analgesia and pain scores for each of the groups at 24 h are shown in *Table 1*. The results at other time intervals were similar and are therefore not shown. At each of the time intervals there was no significant difference between the groups in the

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Table 1 Analgesia requirement and pain scores 24 h after operation and instillation of local anaesthetic

Local anaesthetic solution	Doses of morphine	Doses of Tylex	Pain score
Bupivacaine 0·25 per cent, plain	0 (0–3)	2 (0–12)	4 (2–8)
Bupivacaine 0·25 per cent with adrenaline 0·25 per cent	0 (0–3)	2 (0–8)	3 (2–8)
Bupivacaine 0·5 per cent, plain	0 (0–4)	2 (2–24)	4 (1–8)
Saline 0·9 per cent	0 (0–3)	2 (0–12)	4 (1–8)
P	0·73	0·89	0·71
χ^2	8·7	18·2	17·0
d.f.	12	27	21

Values are median (range)

number of doses of morphine (at 24 h, χ^2 = 8·7, 12 d.f., P = 0·73) or Tylex (at 24 h, χ^2 = 18·2, 27 d.f., P = 0·89) or pain scores (χ^2 = 17·0, 21 d.f., P = 0·71). There was also no significant difference in the time to return to normal activity or work between the groups, and to date there have been no recurrences.

Discussion

In laparoscopic hernia repair the systemic absorption of bupivacaine inserted into the preperitoneal space is slight and well within the non-toxic range[11]. This suggests that the majority of the drug is rapidly bound locally to receptors in the preperitoneal space. Confining the local anaesthetic to the 'wound' caused by the preperitoneal dissection might theoretically result in the majority of the drug being fixed locally and a greater reduction in postoperative pain. However, the present study reveals that this local binding of bupivacaine does not significantly reduce the requirement for postoperative pain relief after laparoscopic hernia repair.

In open hernia repair the addition of adrenaline may enhance the analgesic effect of the local anaesthetic. The present study suggests that this is not so in the preperitoneal space following laparoscopic hernia repair, possibly because the systemic absorption of bupivacaine from this space is unaffected by adrenaline[11]. Similarly, increasing the concentration of bupivacaine to 0·5 per cent does not significantly reduce postoperative pain requirement.

The lack of benefit from local anaesthetic in this study may be related to postoperative pain following laparoscopic procedures being comprised of parietal, diaphragmatic and visceral components[9]. Although many surgeons try to reduce the parietal component by infiltrating local anaesthetics into the laparoscopic port sites, there is no evidence that this reduces postoperative pain[6]. In the present study, this manoeuvre was therefore not performed, as it would have interfered with assessment of the preperitoneal local anaesthetic. Previous studies have shown that free instillation of local anaesthetic into the peritoneal cavity after laparoscopic cholecystectomy[9,10] and tubal ligation[7,8] may reduce the diaphragmatic component without affecting the other two components. In this study preperitoneal bupivacaine may have reduced the parietal component without affecting either the diaphragmatic or visceral component.

The visceral component is caused by diffusion of carbon dioxide into the bowel[9,12]. The disappointing results from instilling local anaesthetic into either the port sites or peritoneal cavity following laparoscopic surgery may be due to the failure to eliminate this component of pain after laparoscopy[6–10]. In the present study patients complained more of visceral discomfort than pain in either the port or hernia sites. This might explain why using preperitoneal local anaesthetic alone had no significant effect on postoperative pain requirement.

It is likely that the reduction in pain after laparoscopy will require techniques that address a combination of the parietal, diaphragmatic and visceral components. Further studies, incorporating local anaesthetic injection of the port sites, laxatives or non-steroidal anti-inflammatory drugs, are therefore required to assess ways of reducing pain after laparoscopy. In the interim, the sole use of preperitoneal local anaesthetic has no significant effect on postoperative pain requirements following laparoscopic hernia repair and its routine use cannot be recommended.

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British Journal of Surgery 1998, **85**, 1015–1019

Correspondence

The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Tracheobronchial lesions following oesophagectomy: prevalence, predisposing factors and outcome

Sir

I read with interest the recent paper by Bartels *et al.* (*Br J Surg* 1998; **85**: 403–6).

I am concerned about the frequent use of the term 'tracheobronchial fistula' in the text and legends. A fistula is an abnormal communication between the lumen of one viscus and the lumen of another[1]. Surely the lesions referred to in the article are pathological communications between the tracheobronchial tree and the mediastinum and/or the pleura.

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1 Tumours, cysts, ulcers, sinuses. In: Bailey and Love. *Short Practice of Surgery*. 20th ed. London: HK Lewis, 1988: 116.

Rationing and surgery: setting boundaries

Sir

Interesting points were raised about rationing in surgery in this leading article by Mr New (*Br J Surg* 1998; **85**: 291–2) and it was rightly stated that 'cosmetic surgery' is a poorly understood term. The article discussed the apparent triviality of procedures such as liposuction, breast reduction and rhinoplasty and their relevance in the NHS. In this context most aesthetic procedures such as those discussed are performed for psychological reasons *and* the physical benefit of the patient.

Breast reduction, for example, is helpful in reducing physical discomfort such as back and neck pain[1] and may facilitate breast cancer detection[2]. Liposuction is used in the treatment of conditions as diverse as gynaecomastia[3], lymphoedema[4], lipodystrophy, hemifacial atrophy[5], lipomas and the debulking of surgical flaps. Rhinoplasty can also provide functional improvement in breathing. It would, therefore, be helpful to discuss rationing in terms of the condition that is to be treated rather than the surgical procedure itself, i.e. the management of minimally ptotic breasts rather than breast reduction or mastopexy and the management of acquired contour deformities rather than liposuction.

This is still not a perfect solution, but this approach may prevent an existing trend in the NHS to ration procedures that may provide significant physical, functional and psychological benefit.

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Genetic alterations in chronic pancreatitis: evidence for early occurrence of *p53* but not K-*ras* mutations

Sir

I read with interest the paper by Gansauge *et al.* (*Br J Surg* 1998; **85**: 337–40) regarding the absence of K-*ras* mutations in chronic pancreatitis. The differential diagnosis of chronic pancreatitis and pancreatic cancer can still present problems in certain patients. It can be particularly difficult to detect a carcinoma within pre-existing chronic pancreatitis. The risk of developing pancreatic cancer is said to be higher in patients with chronic pancreatitis[1] and it is therefore of potential practical importance to be able to detect changes of neoplasia in such patients. If K-*ras* mutations were absent in chronic pancreatitis this may prove a useful tool as the mutation is present in 75 per cent[2] to 90 per cent[3] of pancreatic ductal adenocarcinomas. One of the series quoted by the authors is that of Van Laethem *et al.*[4], but this group have, more recently, published a report of K-*ras* mutation in 19 of 76 (25 per cent) patients with chronic pancreatitis[5]. This important finding needs clarification since patients with chronic pancreatitis may represent those at high risk of developing pancreatic cancer, although the proportion is obviously higher than one would expect.

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Bile duct injury during laparoscopic cholecystectomy without operative cholangiography

Sir
We read with interest the prospective audit of bile duct injury during laparoscopic cholecystectomy by Wright and Wellwood (*Br J Surg* 1998; 85: 191–4). The authors' conclusion, that operative cholangiography is not necessary for the safe performance of laparoscopic cholecystectomy, might have been all the more meaningful if cholangiography had actually been undertaken and been demonstrated to be of no benefit. Few surgeons would suport the view that operative cholangiography provides any safeguard against ductal injury as it is no substitute for adequate exposure of the junction of Hartmann's pouch and the cystic duct. There is some evidence to suggest that operative cholangiography may limit the extent of bile duct injury by early detection and avoid exposing the patient to biliary peritonitis.

Routine operative cholangiography enables the surgeon to better interpret all forms of cholangiography. *Fig. 3* is said to reveal a fistulous communication to a right accessory duct but appears to demonstrate an injury to the main right hepatic duct. It is not clear why the authors believe that an operative cholangiogram would not have detected the entry of the cystic duct into or near the right hepatic duct. They were fortunate that the resulting biliary fistula resolved without apparent further complication 3 years after surgery. Of some 40 patients referred for management of bile duct injury to Edinburgh Royal Infirmary over the past 9 years, we have observed one such patient whose isolated right ductal injury was similarly missed at cholecystectomy (without operative cholangiogram). Two subsequent laparotomies culminated in suture ligation of the free end of the divided 'accessory' duct without a cholangiogram. This patient was referred more than 4 years following this last procedure with recurrent episodes of sepsis within the obstructed right duct system and required treatment by means of a right hepatectomy. Such cases serve to underline the importance of early recognition and appropriate management of bile duct injury.

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Author's reply

Sir
I am grateful to Mr Wakefield and Professors Bornman and Garden for their comments. The authors comment that *Fig. 3* indicates that the main right hepatic duct was divided during laparoscopic cholecystectomy. The postoperative endoscopic retrograde cholangiopancreatography (ERCP) was submitted as part of the original paper but the paper was deemed too long and this figure removed. In fact, when we noted that this small duct had been divided we performed a laparotomy and ligated the cut end having carried out an operative cholangiogram which revealed a normal duct pattern with no evidence of any leakage of bile. Several days later when a fistula became apparent ERCP revealed no evidence of contrast leak and that the right main hepatic duct was intact.

We agree that had this been the right main hepatic duct spontaneous closure would have been very unlikely and much larger volumes of bile would have been produced from the fistula. One possibility is that the accessory duct did, in fact, communicate with the right duct system but that this could not be shown on operative cholangiography or ERCP. The duct that was divided was a small accessory duct and the right hepatic duct system was demonstrated after the injury to be intact both on operative cholangiography during laparotomy and on subsequent ERCP.

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Genetic predisposition to breast cancer

Sir
We read with interest the leading article by Mr Odling-Smee (*Br J Surg* 1998; **85**: 147–8) and share his desire for a common management strategy for women at increased risk of breast cancer. The suggested protocol for the management of such women however leaves much to be desired. The sensitivity of annual mammography is reduced in women under 50 years with a family history of breast cancer[1] and annual mammography in these women does not lead to a diagnosis of earlier stage breast cancer than respective a priori risk groups[2]. No clinical trial of mammography has demonstrated a reduction in breast cancer mortality for these women and the cost implications to the NHS of regular screening would be enormous[3]. Monthly self-examination results in the detection of increased numbers of small and node-negative tumours[4,5], but no study has shown an improvement in survival. Regular examination by an experienced clinician has similarly poor results[5,6]. Many screening centres struggle to meet current demands and a large increase in the screened population would take these centres past breaking point. Strategies for breast cancer prophylaxis (including long-term tamoxifen and retinoid supplementation) are the subject of clinical trials but no data have yet been published to support their use in high-risk women.

As the purse-strings of the NHS tighten, it is unacceptable to institute 'hypothetical' and 'empirical' protocols for patient management and the only acceptable long-term management of such women currently is within the boundaries of a randomized clinical trial.

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Author's reply

Sir
I do not disagree with Messrs Byrne and Bundred and was careful to keep away from the financial issue. I have proposed

the development of a common management strategy and the national collection of data but the details are open to discussion. All those who run breast clinics see large numbers of patients referred by GPs for advice about family history. Such is the public demand for this advice that if breast clinics do not provide it someone else will. We can either refuse to see these patients because breast clinics are not funded or we can develop a common strategy and collect information nationally and press for appropriate funding. I would advocate the latter.

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Systemic inflammatory response syndrome

Sir

We congratulate Davies and Hagen on their clear and complete review (*Br J Surg* 1997; **84**: 920–35) of systemic inflammatory response syndrome (SIRS). We write to stimulate discussion regarding the statement 'No directed therapies have been successful to date in influencing outcome' which seems true regarding mediator therapies. We suggest that directed therapy for oedema is a frequently overlooked opportunity.

Oedema that is both general and organ-specific does influence outcome. Oedema after reperfusion injury kills muscle in the calf due to compartment syndrome. Oedema of the brain follows head injury. Oedema within kidney parenchyma responds to decapsulation with restoration of function[1]. Oedema after septic shock complicates recovery.

True, '... secondary MODS [multiple organ dysfunction syndrome] develops ... as a consequence of host response'[2], but physician response is also a factor. Shock requires rapid vascular filling with fluids biased toward the cells and starches that stay in leaky capillaries. Aftershock calls for different fluids and the goal changes from vascular filling to reducing extracellular overfill quickly while preventing new shock.

The following recent developments should increase the interest in oedema and capillary leak. Urine microalbumin parallels general leak and now accurately predicts pulmonary failure and the end of leak[1] as a guide to albumin use. Oedema sharply decreases when a starch stops the leak of albumin from capillaries, probably by plugging pores. The starch used has molecules of medium size and a narrow range of molecular weights. Using this starch, reperfused spinal cords retain function as oedema is controlled[3] and heart muscle survival rate improves 500 per cent after reperfusion[4,5]. Also, vitamin C reduces postburn oedema[6]. For these reasons the existing paradigm of SIRS as a mediator problem only might well be extended to include the renewed consideration of oedema itself in the aggravation and management of SIRS and clinical capillary leak syndrome (CCLS).

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Authors' reply

Sir

The letter by Dr Bascom and colleagues addresses the possibility of modulating the secondary event of tissue oedema which is a sequel to SIRS. Oedema, as illustrated by the various examples cited by the authors, is a manifestation of the loss of integrity within the microcirculation. This is the result of activation of the SIRS cascade of cellular and humoral mediators. The therapeutic interventions suggested by Dr Bascom and colleagues suffer the same weaknesses as those described in our article for mediator modulation. The development of SIRS and secondary MODS are driven by the host's response to the initiating stimulus; the physician generally is playing catch-up in a clinical rollercoaster whose ride is more often than not poorly defined, and any therapies used are aimed at treating effects and not causes. Therefore, we continue to contend that cellular and humoral mediators are primary movers in the pathophysiology of SIRS and would categorize tissue oedema as a consequence of SIRS-induced microcirculatory derangements.

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Randomized clinical trial of conventional cholecystectomy *versus* minicholecystectomy

Letter 1

Sir

Although it is interesting to compare the two approaches in a prospective randomized trial (*Br J Surg* 1997; **84**: 1683–6) the design is unusual and the study raises other issues. The authors state that (in February 1997) there had been only one study comparing mini- and laparoscopic cholecystectomy, when there have been three major trials in the UK alone[1–3]. We were surprised to learn that 'under the present German national health system patients undergoing such operations are required to have a minimum stay in hospital of 11 days'. If this is so, it largely negates any attempt to shorten hospital stay by improving surgical techniques. The purpose of the study was to compare pain but, surely, it is unethical to allow patients after straightforward operations to have severe pain or even moderate pain. It is not stated whether local anaesthetic was infiltrated in the wounds. Moss[4] has shown that with good local infiltration 99 per cent of patients having an open cholecystectomy do not need opiates. Ortega *et al.*[5] found that with good analgesia patients with traditional open procedures went home at a median of 1·1 days compared with 1·3 days for laparoscopic procedures. In our own randomized trial comparing mini- and laparoscopic procedures, the patients experienced mild or no pain after operation[6].

It is very difficult to see how the authors can conclude that 'minicholecystectomy cannot be regarded as a true alternative to the superior laparoscopic technique' when they have not compared the two or even reviewed the existing trials.

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1 McMahon AJ, Russell IT, Baxter JN *et al.* Laparoscopic *versus* minilaparotomy cholecystectomy: a randomised trial. *Lancet* 1994; **343**: 135–8.
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3 Majeed AW, Troy G, Nicholl JP *et al.* Randomised, prospective, single-blind comparison of laparoscopic *versus* small-incision cholecystectomy. *Lancet* 1996; **347**: 989–94.
4 Moss G. Raising the outcome standards for conventional open cholecystectomy. *Am J Surg* 1996; **172**: 383–5.
5 Ortega AE, Peters JH, Incarborne R *et al.* A prospective randomised comparison of the metabolic and stress hormone responses of laparoscopic and open cholecystectomy. *J Am Coll Surg* 1996; **183**: 249–56.
6 Squirrel D, Majeed AW, Troy G *et al.* A randomised, prospective, blind, comparison of postoperative pain, metabolic response and perceived health after laparoscopic and small-incision cholecystectomy. *Surgery* (in press).

Letter 2

Sir

The clinical trial by Schmitz *et al.* comparing mini- and conventional cholecystectomy led to a conclusion that 'minicholecystectomy cannot be regarded as a true alternative to the superior laparoscopic technique'. This is illogical as laparoscopic cholecystectomy was not included in this study.

In minilaparotomy, the length and the location of the incision should be defined. Since 1990, we have performed micro- and minilaparotomy cholecystectomy in 2012 unselected patients. Some 92·5 per cent had a 4-cm single microlaparotomy incision[1,2], 7·1 per cent had a 6-cm minilaparotomy, and 0·2 per cent had an 8-cm classic minilaparotomy incision. Four patients had a 'classic' cholecystectomy.

In a randomized study of 270 patients in each arm, postoperative pain and ambulation was compared in laparoscopic cholecystectomy *versus* microlaparotomy cholecystectomy and no significant difference was found[4].

In our international courses, we teach that the short incision, its location and specific instrumentation contribute to decreased pain, quicker recovery and reduced cost. Schmitz *et al.* use a subcostal incision transecting muscles involved in respiration thereby creating excessive pain. The 4-cm vertical midline incision at the lower edge of infrasternal triangle provides reduced pain and better exposure[3,5].

In the 2012 patients, common duct injury occurred in only three patients. The mean operating time in 512 simple procedures was 18 min, and in 1500 complicated procedures, 35 min.

We observed no haematoma and consider low-dose heparin contraindicated. Sequential compression stockings may be used. Three patients (0·014 per cent) died within 30 days.

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1 Rozsos I. A minimálisan invazív cholecystectomia alternatívái. *Orv Hetil* 1993; **134**: 1083–8.
2 Rozsos I, Jakó G. Microlaparotomy cholecystectomy. *Ann Surg* 1995; **222**: 762–3 (Letter).
3 Rozsos I, Jakó G. Randomized trial of laparoscopic cholecystectomy and mini-cholecystectomy. *Br J Surg* 1996; **83**: 708 (Letter).
4 Rozsos I. Micro and modern minilaparotomy in biliary tree surgery. *Orv Hetil* 1996; **137**: 2243–8.

Letter 3

Sir

Schmitz *et al.* suggest that minicholecystectomy cannot be considered as an alternative to laparoscopic cholecystectomy. They compared minicholecystectomy, not with laparoscopic cholecystectomy but, surprisingly, with open cholecystectomy, which weakens the argument. A parametric statistical test (Student's *t* test) was used to compare differences in visual analogue scale (VAS) scores for pain instead of a non-parametric method suitable for an ordinal scale. More serious is that the pain scores were grouped into slight, moderate and severe, and thereafter the tests were made within these groups. This makes the differences between the two types of operation smaller. The graphs in *Figs 1* and *2* are deceptive as a large difference in VAS scores between groups could still lead to graphs that show no difference. Additionally, how can the mean VAS score for patients with severe pain undergoing minicholecystectomy be 6·46 and 6·29 respectively when severe pain is defined as a VAS score between 7 and 10?

Finally, *Fig. 3* suggests that open cholecystectomy is associated with more pain than minicholecystectomy as for each postoperative day the analgesia requirement is greater for the open cholecystectomy group. Instead of comparing the total analgesia requirement for the two groups, the authors studied each postoperative day separately. With only 65 patients in each group the power to find any significant difference by such an approach is very low. No significant difference certainly does not mean that the two groups are necessarily equal. The conclusions drawn by the authors are not justifiable from the study.

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Authors' reply

Sir

The aim of our study was to evaluate the amount of analgesic medication required by patients after minicholecystectomy or conventional cholecystectomy. It showed that the group of patients undergoing minicholecystectomy were free from pain after the operation 2 days earlier (i.e. slight pain, VAS between 0 and 3) as compared with the group of patients undergoing conventional cholecystectomy. The comparison of the total analgesia requirement for both groups did not show any significant difference. Furthermore, it was not the authors' intention to compare the results of the minicholecystectomy group with the results of any laparoscopically cholecystectomized group of patients.

Rozsos *et al.* in their comment try to compare their own results with this study. It has to be recognized that they cholecystectomize patients through a vertical midline incision, which is not a common practice and requires specially designed instruments for this procedure to prevent long incisions. While their data concerning this procedure might be of interest they cannot be used because of the above-mentioned circumstances in a comparative assessment of the results of our study.

Johnson and Majeed mention three randomized studies comparing laparoscopic cholecystectomy with minicholecystectomy. Our study did not intend to make a direct comparison between mini- and laparoscopic cholecystectomy. Rather the principal interest was to determine which of the open cholecystectomies should be considered as a standard technique. The results attained from this standard procedure can then be rightfully compared with those of laparoscopic cholecystectomy. The standard procedure would also be the defined interchange operation.

In our opinion it is not useful to refer to randomized studies that do not focus on the value of minicholecystectomy. In many randomized studies the advantages of preoperatively applied low-dose heparin could be demonstrated, lowering the rate of deep vein thrombosis, especially after general anaesthesia. Furthermore, the *Deutsche Gesellschaft für Chirurgie* strongly recommends heparinization before abdominal procedures. It is therefore incorrect to ignore this high standard, especially during a randomized study as suggested in Rozsos *et al.*'s commentary.

The analgesic medication used by patients consisted of paracetamol *ad libitum*, and was sufficient to lower the perceived level of pain to a minimum. Concerning postoperative pain the superiority of laparoscopic cholecystectomy has to be mentioned as many randomized studies could demonstrate lower pain levels after laparoscopic cholecystectomy compared with other techniques.

The day of discharge for the patient is very often used in studies as an argument for or against an operative procedure. To register the complications occurring after operation for scientific reasons the patient has to be observed for at least 14 days.

The perceived level of pain, its treatment, different health insurance systems, different cost structures and the patient's will influence and decide the day of discharge today in Germany. The influence of the operative procedure on the actual day of discharge has a secondary role. It was therefore important for this study and possible to monitor all patients for 10 days. The perceived level of pain was measured with the VAS. Slight pain was defined as 0 to 3, moderate pain as 3 to 6 and severe pain as 6 to 10 on the VAS, and not 7 to 10 which was a misprint in our study. We thank Dr Iselius for recognizing this anomaly.

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Book reviews

Textbook of Surgery. The Biological Basis of Modern Surgical Practice. 15th ed. (CD-ROM – Single User Version)

D. C. Sabiston Jr (ed.). 1998. Philadelphia, Pennsylvania: WB Saunders. £110.

'Sabiston' is one of the standard surgical textbooks and it was a pleasure to explore it using this new format. The disk is essentially an on-screen version of the book, with appropriate indexing, searching and linkage software to enable rapid access throughout the text. There are no additional features of content, however, which seems to be an opportunity missed. This disk is certainly among the front runners for the CD-ROM market being a direct competitor to the *Oxford Textbook of Surgery*. Reference libraries (institutional or departmental) with appropriate access terminals and accumulating a CD-ROM section will probably have both disks. Individual surgeons will probably choose one or other product. The text is easy to read and up to date. The search and indexing systems work well, enabling rapid access to appropriate sections of text, and it is possible to highlight and print sections of text and tables. I was disappointed not to be able to download illustrations. I enjoyed looking at this disk and will certainly return to it when searching for up-to-date reference material outside my specialist field of interest

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Trauma

I. Greaves, J. M. Ryan and K. M. Porter (eds). 245 × 188 mm. Pp. 421. Illustrated. 1997. London: Arnold. £47.50.

This is the first volume in what intends to be a series covering topics 'across the whole spectrum of trauma' which the Editors hope 'will allow people to remain up to date outside their own particular field of specialist expertise'. The editors are British and the editorial and advisory boards are composed of 'traumatologists' from around the world. Only seven of the 58 contributors to this volume, however, work outside the UK. The book has 11 sections and 36 short chapters covering a wide spectrum of trauma-related topics, such as air safety, disaster mitigation, prehospital analgesia, paramedic training, what constitutes a trauma surgeon, emergency and definitive care, rehabilitation and land mines. The style of the book is refreshing and easy to read. Chapter 16 on hypotensive resuscitation is superb and the brief historical notes on Colles (the fracture) and Thomas (the splint) are excellent. Only British doctors could write a chapter on 'Doctor in . . . acting'; only they would understand it. This is entertaining and valuable reading for anyone involved in the care of patients with trauma, be it doctors, nurses or paramedics. The authors succeeded in what they set out to do; one would only hope that the next volumes include more international contributors.

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Imaging of Anorectal Diseases

S. M. Hussain (ed.). 333 × 213 mm. Pp. 148. Illustrated. 1997. London: Greenwich Medical Media. £69.50.

Imaging of Anorectal Diseases is a beautiful book. It contains good pictures of magnetic resonance imaging (MRI) scans, endosonographs and proctographs. It also gives a helpful overview of diagrams to explain the pictures. The first three chapters give an impression of the normal anatomy of the anorectum depicted with various imaging techniques. MRI with endoanal and endorectal coils, as well as endosonographs, give very good pictures of anatomy and pathological findings. The only problem is that one has to disturb the normal anatomy by introducing an endoanal device. Probably new developments with phased-array and surface coils will give even more accurate anatomical images. The findings with anal fistulas, perineal Crohn's disease and tumours are convincing. In two chapters the authors outline the place of radiological imaging techniques in detecting causes of faecal incontinence and other functional disorders. This book is of great value for colorectal surgeons and is a guideline for radiologists dealing with anorectal disorders. In a comprehensive way it gives information that cannot be found in general textbooks.

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Surgical Management of Cutaneous Ulcers and Pressure Sores

B. Y. Lee and B. L. Herz (eds). 260 × 180 mm. Pp. 263. Illustrated. 1997. New York: Chapman and Hall. £65.

Recognition of the disability and cost to health care systems of patients with ulcers has spurred renewed interest in the management of these conditions. This tends to be a multispecialty and multiprofessional problem involving both the community and hospitals. There have been very few good publications in this area bringing together all the aspects of care of these patients. As such, this book makes a welcome addition. Contributions from 21 authors, all based in North America, cover an enormous range of topics, including the biology of wound healing and the role of nutrition, aspects of nursing care, and assessment of pressure ulcers as well as specialized plastic surgical procedures. Much of the clinical practice and health economics are based on American experience, but this does not greatly diminish its interest to a European reader. A large part of the book relates to pressure ulcers and these sections are well worth reading. Probably due to breadth of ground covered, and despite the title, I found it hard to understand at whom the book was aimed. Some subjects, such as the biology of wound healing and fasciotomy of the diabetic foot, are covered in great detail, while others, in particular the management of patients with arterial disease, were brief to the point of being of little value. It would have been helpful to have had a more uniform level of knowledge throughout the book. Similarly, there tends to be a lot of repetition between contributors. For instance, the aetiology of venous ulceration is discussed on at least three separate occasions. In summary, anyone involved in the care of patients with ulcers will find something of interest in this volume. However, I think the wide variation in the level of knowledge presented limits its value, making it neither a specialized handbook nor a broad overview.

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Hepatobiliary and Pancreatic Surgery. Imaging Strategies and Surgical Decision Making

S. R. T. Evans and S. M. Ascher (eds). 260 × 183 mm. Pp. 569. Illustrated. 1998. New York: Wiley-Liss. £100.

In the past two decades major developments in both surgery and imaging procedures for hepatobiliary and pancreatic diseases have been made. For a hepatobiliary and pancreatic surgeon it is essential to understand the advantages and disadvantages of each of the different imaging studies. This book, written by American radiologists and surgeons, is a hybrid medical text between the two specialties with reviews for the anatomic sections. It is divided into four main anatomic sections: gallbladder, biliary tree, liver and pancreas. Each section is subdivided into different chapters that focus on the different imaging techniques. Even new imaging studies, such as MRCP, are described and explained extensively; these chapters are written by radiologists. Every chapter finishes with a surgical summary, written by surgeons.

In each of the subtitled chapters different disorders are featured. First, epidemiological data are presented, followed by thorough discussion of advantages and disadvantages of the imaging technique in question. The surgical summary gives a good idea what a surgeon needs to consider and which technique is most helpful to obtain the necessary information. The practitioner is directed through the assessment of patients with specific diseases by the help of flow diagrams. This is one of the reasons why this book is especially useful not only for experienced hepatobiliary and pancreatic surgeons but also for residents and junior practitioners. The volume is well illustrated with an ample number of black and white illustrations. Numerous original pictures are explained; helpful sketches are added. This book is aimed at hepatobiliary and pancreatic surgeons at every educational level. With its detailed descriptions it may be a stimulus even for experienced surgeons to consider special indications for imaging studies in their patients. In times of restrained financial resources it is even more important to reduce unnecessary and expensive diagnostic tests. The diagnostic investigation as suggested in this book will certainly help to render diagnostic strategies more efficient and then more cost-effective. This detailed and well illustrated book should become an every-day tool in the assessment of patients with hepatobiliary and pancreatic disorders.

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Scientific Surgery

The British Journal of Surgery is committed to practice of surgery based on scientific evidence. Each month we will publish a list of randomized trials and meta-analyses collated from English language publications. A collection of all these papers will be available in the Scientific Surgery Archive which will be held on *The British Journal of Surgery* website together with links to free Medline sites where the full papers can be accessed (see below for details). If you have published a recent randomized trial which has not been featured in Scientific Surgery, the Editors would be pleased to receive a reprint and consider its inclusion.

Randomized trials

Mishihira T, Hirayama K, Mori S. A prospective randomised trial of extended cervical and superior mediastinal lymphadenectomy for carcinoma of the thoracic esophagus.
Am J Surg 1998; **175**: 47–51. (UGI-oesophagus)
A study of 62 patients in which 2- and 5-year survival rates were not significantly different.

Benedetti E, Coady MT, Asolati M, Dunn T, Stormoen B, Bartholomew A *et al.* A prospective randomised clinical trial of perioperative treatment with octreotide in pancreatic transplantation.
Am J Surg 1998; **175**: 14–17. (UGI-pancreas)
Octreotide significantly reduced the overall rate of major complications from three of seven to zero of ten untreated patients.

Staubach K-H, Schroder J, Stuber F, Gehrke K, Traumann E, Zabel P. Effect of pentoxifylline in severe sepsis: results of a randomized, double-blind, placebo-controlled study.
Arch Surg 1998; **133**: 94–100. (General)
Fifty-one intensive care patients were studied. Pentoxifylline significantly improved cardiopulmonary dysfunction but had no effect on survival.

Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM, Clark DE. Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial.
J Trauma 1998; **44**: 50–8. (General)
Hypertonic saline used instead of Ringer's lactate did not affect outcome in this study of 34 patients.

Miller PR, Meredith JW, Chang MC. Randomized, prospective comparison of increased preload *versus* inotropes in the resuscitation of trauma patients: effects on cardiopulmonary function and visceral perfusion.
J Trauma 1998; **44**: 107–11. (General)
Visceral perfusion was improved in patients managed by increasing fluid preload; the study involved 39 patients.

Carapeti EA, Kamm MA, McDonald PJ, Phillips RKS. Double blind randomised controlled trial of effect of metronidazole on pain after day-case haemorrhoidectomy.
Lancet 1998; **351**: 169–72. (LGI-anus)
In this trial including 40 patients, postoperative metronidazole 400 mg three times daily for 7 days reduced pain significantly on days 5–7 after surgery, increased patient satisfaction and allowed earlier return to work.

Rhodes M, Sussman L, Cohen L, Lewis MP. Randomised trial of laparoscopic exploration of common bile duct *versus* postoperative endoscopic retrograde cholangiography for common bile duct stones.
Lancet 1998; **351**: 159–61. (UGI-biliary)
Eighty patients with bile duct stones identified during laparoscopic cholecystectomy were randomized: primary duct clearance was achieved in 75 per cent of each group.

Hanna GB, Shimi SM, Cuschieri A. Randomised study of influence of two-dimensional *versus* three-dimensional imaging on performance of laparoscopic cholecystectomy.
Lancet 1998; **351**: 248–51. (UGI-biliary)
No advantage found for 3-D imaging by specialist registrars doing 80 operations.

Younes RN, Yin KC, Amino CJ, Itinosche M, Rocha-e-Silva M, Birolini D. Use of pentastarch solution in the treatment of patients with haemorrhagic hypovolaemia: a randomized phase II study in the emergency room.
World J Surg 1998; **22**: 2–5. (General)
In this study of 23 patients, pentastarch was as effective as isotonic saline.

Robeer GC, Brandsma JW, van den Heuvel SP, Smit B, Oostendorp RAB, Wittens CHA. Exercise therapy for intermittent claudication: a review of the quality of randomised trials and evaluation of predictive factors.
Eur J Vasc Endovasc Surg 1998; **15**: 36–43. (Vascular)
Ten studies were evaluated, all showed the significant benefit of exercise.

The British Journal of Surgery website can be found at: http://www.bjs.co.uk. In addition to details of current and previous articles featured in Scientific Surgery, the website contains details of the Editorial Team and Board, instructions to prospective authors, links to other sites (such as The Cochrane Library) and forthcoming surgical events. The Editors welcome comments and suggestions about our website, either in writing or through the website address.

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Following final approval of articles, you will be asked to submit the accepted version on disk. These should be IBM-compatible. An accurate hard copy must accompany each disk, together with details of the type of computer used, software, and disk system if known. **Do not justify.** Please send us digital versions of your figures. Ideally, these should be sent in native format or WMF if created in Windows. Files saved as PS, EPS, GIF and TIF may also be used, but please note that it may not be possible to modify them. Avoid using tints if possible; if they are essential, try to make them coarse. Further details can be obtained from the publisher. Disks will not be returned to authors.

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The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts, which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *New England Journal of Medicine* 1997; **336**: 309–15, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, *British Medical Journal*, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1.00 per copy).

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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The Editors welcome topical correspondence relating to articles published in the Journal. Letters should not exceed 250 words and should be typed double-spaced.

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Manuscripts must be clearly reproduced with adequate space for editorial notes. **Type or print the text on one side of sheets of A4 paper (210 × 297 mm) with double spacing and 4-cm margins. Manuscripts that do not conform to these requirements will be returned to you for recasting.** Begin each section (abstract, introduction, patients and methods, results, and discussion) on a new page.

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On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review etc.).

Abstract

This should be not more than 200 words on the second page of the manuscript and be presented in a structured format. **Background:** state why the study was done, and its main aim; **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study: randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings of the study; include important numerical values. **Conclusion:** state the main conclusion drawn from the results. Controversial or unexpected observations may be highlighted, but keep this section brief. Write the abstract in clear prose.

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Abbreviations

Use abbreviations sparingly. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension by the reader. Use abbreviations consistently throughout the text and clearly define each one on first use.

Numbers and units

Use the decimal point, not a comma, e.g. 5·7. Use a space and not a comma after thousands and multiples thereof, e.g. 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, give the actual values and units, with SI equivalents inserted in parentheses at appropriate points.

Statistics

For detailed guidance on the handling of statistical material, consult *Br J Surg* 1991; **78**: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen end-points, and explain the rationale for the choice of sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; **276**: 637–9).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. Do not use the '±' symbol; these statistics should be presented in parentheses after the mean value.

Analysis

Clearly describe which methods were used for which analyses; any methods not in common usage should be supported by references. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value, e.g. '$t = 1·34$, 16 d.f., $P = 0·20$'.

Actual *P* values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant'. Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Do not confuse statistical significance with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data.

References

Type the references with double spacing in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged. Reference to unpublished communications will not be accepted. Cite personal communications in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, number the references consecutively by superscript: ^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation is quoted); year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66**: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer, 1981: 123–63.

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Leading articles

Role of lymphadenectomy in the treatment of differentiated thyroid carcinomas

Papillary thyroid cancer (PTC) is the most common form of thyroid carcinoma. It has a comparatively good prognosis and, therefore, before conclusions can be drawn about the merit of any particular operation, patients must be followed over decades. Surgical complications have carried great weight in the discussion about how radical the surgical treatment should be, but complications nowadays are rare. The discussion of whether total thyroidectomy or lesser procedures should be the treatment for thyroid carcinomas was protracted. Now, reasonable agreement exists that total or near-total thyroidectomy is the best treatment and the focus of the discussion has moved to the treatment of node metastases. The disagreement concerning the treatment of node metastases is pronounced when it comes to PTC.

The argument supporting a radical approach to node excision is that the presence of node metastases lowers the survival rate. Advocates for a conservative approach think that little association exists between node metastases and death from thyroid carcinoma. Both factions base risk calculations on the node status *before* operation. If it is presumed that the presence of lymph node metastases is a risk factor for death, then a radical node dissection would attenuate or abolish the association between the occurrence of preoperative node metastases and premature death. If less radical operations are done, a smaller proportion of the patients with lymph node metastases will have these diagnosed which makes a fair calculation of the risk of preoperative lymph node metastases impossible. Basing the risk calculation on the incidence of node metastases left after operation would be more logical, if it were possible. To obtain an unequivocal answer to the question of whether a reduction of node metastases makes a difference to outcome would require a randomized study. If such a study were possible, it would take more than a decade to provide the answer.

The only currently available method is to compare survival in patients who are similar in all aspects other than the treatment of node metastases. Two such Scandinavian studies exist. In one, node-picking was the procedure used to treat node metastases[1,2]. In the other, a meticulous node dissection of the central neck region was performed in 90 per cent of patients and a lateral neck dissection only if macroscopic lateral node metastases were found[3]. In the node-picking series 8 per cent of the patients were excluded from the analysis because they were not radically treated, the death rate was 9 per cent and the recurrence rate was 23 per cent after a median observation of 7·3 years[2]. In the other series[3] the results were updated in March 1998 when the death rate was 2 per cent and the recurrence rate was 6 per cent after a median observation of 15·6 years.

In 1988 there was a recommendation that patients in whom residual tumour remained after resection should not be included in the calculation of recurrence rate[4]. Many groups have subsequently excluded this kind of patient from survival analyses[2,5]. No distinction exists between persistent and recurrent disease. If this kind of exclusion were accepted, subjective influence on the analysis would be introduced, making comparisons between patient series difficult or impossible. Exclusion of patients with distant metastases would be appropriate when evaluating the results of local therapy.

Grant *et al.*[4] defined local recurrence of PTC as tumour in the resected thyroid bed, thyroid remnant or other adjacent tissues of the neck. Lymph node metastases were classified as a separate entity. Fifty per cent of their patients with local recurrence died from PTC. According to these authors very few patients die from PTC when neck nodal metastases represent the first recurrence. The tumour tissue in a node metastasis can grow and destroy the typical lymph node histology, leading pathologists to think that separating a node metastasis from other local recurrences can be impossible. This means that node metastases can cause more deaths than is apparent when the patients are grouped according to the scheme of Grant *et al.*[4].

Sporadic medullary thyroid carcinoma (MTC) is usually unilateral while hereditary MTC has a bilateral distribution. Node metastases from MTC have deleterious effects on survival[6]. Both central and lateral node metastases usually occur in patients with palpable MTC, while patients with non-palpable hereditary MTC with few exceptions have only central node metastases. Most agree that total thyroidectomy and central lymph node dissection should be carried out for this condition. The handling of the lateral node metastases should be based on their known distribution[7,8].

Following this scheme for primary treatment of patients with MTC, the result for 50 patients with hereditary MTC, 60 per cent of whom had node metastases, was one death during a mean observation of 15 years. Meticulous extended lymphadenectomy has been used also in patients with persistent and recurrent MTC with normalization of calcitonin levels in one-third of the patients and with a substantial reduction in another 40 per cent of patients. In some patients with pain or diarrhoea the use of this technique has resulted in resolution of symptoms[9,10].

The meticulous surgical technique that has been effective in reducing or normalizing the tumour marker, calcitonin, in MTC[9,10] has been applied to PTC with excellent results[3]. The author's experience and most arguments speak in favour of total thyroidectomy and a meticulous central neck dissection as the treatment of choice for PTC. The central dissection is done because most lymph node metastases occur in that area. Central metastases are most detrimental for survival and there is a greater risk of complications at repeat operations in the central area. There is no need for a routine lateral dissection in PTC.

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Intra-abdominal hypertension and the abdominal compartment syndrome

As long ago as 1951 M. G. Baggot, an anaesthetist from Dublin, suggested that forcing distended bowel back into an abdominal cavity of limited size may kill the patient[1]. He had conceived that the factor leading to the high mortality rate associated with abdominal wound dehiscence is not the dehiscence itself but the emergency procedure to correct it that produces intra-abdominal hypertension (IAH). But even then Baggot may have been re-inventing the wheel as the adverse physiological effects of IAH have been repeatedly described since the 19th century[2]. These reports, as well as more recent studies documenting the respiratory[3], haemodynamic[4] and renal[5] compromise caused by IAH, were largely ignored by the surgical community. The 1990s, however, generated a large number of experimental and clinical studies to promote the notion that IAH, resulting in an abdominal compartment syndrome (ACS), is a common and clinically significant entity in critically ill surgical and traumatized patients[6].

An increase in the volume of any of the abdominal or retroperitoneal contents increases intra-abdominal pressure (IAP) which, at the bedside, is best measured via a urinary bladder catheter connected to a manometer or pressure transducer. As IAP is transmitted to adjacent spaces and cavities, it adversely affects cardiac output, pulmonary ventilation, renal function and cerebrospinal pressure. Furthermore, increased IAP is associated with a reduction in visceral perfusion; a strong correlation has been found between increasing IAP and a decrease in splanchnic blood flow, as shown by a reduction in intramucosal pH of the gut[7].

Deleterious consequences of raised IAP appear gradually. At pressures of less than 10 mmHg, cardiac output and blood pressure are normal but visceral arterial blood flow falls significantly; an IAP of 15 mmHg produces adverse cardiovascular changes, and an IAP of 20 mmHg may cause renal dysfunction and oliguria, while an increase to 40 mmHg induces anuria. In an individual patient, the effects of increased IAP are not isolated but usually superimposed on multiple underlying and coexistent factors, the most notable being hypovolaemia, which aggravates the effects of increased IAP. ACS consists of increased inspiratory pressures, decreased cardiac output and oliguria, in spite of apparently 'normal' or increased cardiac filling pressures[8]; it is observed in patients with an IAP above 25 mmHg.

Clinically significant IAH has been observed in a variety of contexts, such as postoperative intra-abdominal haemorrhage, complicated abdominal vascular procedures, operations such as hepatic transplantation, severe abdominal trauma (accompanied by visceral swelling, haematoma or the use of abdominal packs), severe peritonitis, acute pancreatitis, the use of a pneumatic antishock garment, peritoneal insufflation during laparoscopic procedures and tense ascites in patients with cirrhosis[6,7]. The liberal measurement of IAP allows the recognition of IAH with increasing frequency in daily clinical practice. Cardiovascular collapse or respiratory failure in patients with an abdominal catastrophe, previously attributed to septic shock, hypovolaemia or premorbidity compromised organ systems, may now occasionally be explained by the coexistence of IAH. In most instances the adverse effects of IAH cannot be separated from the underlying disease. Is the patient with intestinal obstruction and an IAP of 25 mmHg moribund because of hypovolaemia, endotoxaemia or IAH? Probably all of these work in concert and need to be addressed.

That extreme cases of ACS require immediate attention is obvious. But what about moderate increases in IAP compensated by appropriate fluid and ventilatory therapy? A prospective study has identified IAP over 20 mmHg in a third of patients who are undergoing abdominal surgery. Postoperative IAH correlates significantly with the incidence of renal dysfunction and death[9]. The authors believe that the detrimental physiological effects of IAH take place long before the manifestation of ACS becomes clinically evident, just as nerve and muscle ischaemia begins long before neuromuscular signs of the extremity compartment syndrome are evident. In our experience, IAH is common after major abdominal trauma. It may cause gut mucosal acidosis at lower bladder pressures, long before the onset of clinical ACS. Uncorrected, it may lead to splanchnic hypoperfusion, distant organ failure and death. Prophylactic non-closure of the abdomen may aid the prevention, early recognition and treatment of IAH, and reduce these complications[10].

Clinically significant IAH resulting in an ACS should be managed by abdominal decompression. However, the decision to decompress the abdomen should not be based on isolated measurements of IAP without considering the whole clinical circumstance. Early or mild physiological abnormalities caused by increased IAP can be altered by fluid administration or afterload reduction. Decompression in established ACS, however, restores normal physiology when performed in the well resuscitated patient. To prevent haemodynamic decompensation, intravascular volume should be restored, oxygen delivery maximized, and hypothermia and coagulation defects corrected. Following decompression, the abdominal skin and fascial edges are left open, using one of the temporary abdominal closure methods that have been described[6].

The key issue, however, is prevention. To avoid IAH and ACS, forceful closure of the abdomen in patients with massive retroperitoneal haematoma, visceral oedema, severe intra-abdominal infection or a need for haemostatic packing should be avoided. Postoperative evisceration is a sign of IAH and managing it with fascial reclosure under tension is a recipe for a high morbidity rate. Intraoperative measurement of IAP, with the fascial edges temporarily approximated, provides an indication of whether formal abdominal closure is advisable.

That severe IAH is harmful and needs to be addressed is indisputable, but is limited IAH a marker of critical surgical illness or significant co-morbidity? Longitudinal studies of a large number of surgical and traumatized patients are needed to allow a better understanding of the natural history and clinically significant effects of mild and moderately raised IAP before routine decompression for non-dramatic IAH can be recommended. Meanwhile this old-new pathophysiological entity, which has been ignored for so long, should be recognized, prevented and treated.

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Review

Physiological and functional outcome following ultra-low anterior resection with colon pouch–anal anastomosis

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Background Low rectal cancer is usually managed by ultra-low anterior resection (ULAR) with total mesorectal excision and straight coloanal anastomosis. However, following this procedure patients often suffer from frequency, urgency of bowel action and, occasionally, faecal incontinence. To overcome such problems, a colon pouch may be fashioned and a subsequent colon pouch–anal anastomosis performed. The physiological and functional outcome following the use of a colon pouch are appraised.

Methods All relevant papers identified from a Medline search and papers from cross-referencing were reviewed.

Results and Conclusion Creation of a colon pouch following ULAR results in reduced bowel frequency, and a lower incidence of urgency and faecal incontinence. Although there is a slightly increased incidence of evacuatory disorder and need for enemas or suppositories, this appears to be a minor problem which may possibly be overcome by using a smaller colon pouch. Compared with straight coloanal anastomosis following ULAR, the creation of a colon pouch produced a superior functional outcome.

Rectal cancer remains one of the commonest cancers in many countries; in the UK it is the second commonest malignancy after lung cancer. For many decades surgical thinking and practice was dominated by the teaching of Sir Ernest Miles[1,2] which, for middle and low rectal cancers, meant abdominoperineal resection (APR) of the rectum with a permanent colostomy. Surgical practice has changed dramatically since Miles' time. Most patients undergoing potentially curative resection now have restoration of intestinal continuity and preservation of the anal sphincter by means of an ultra-low anterior resection (ULAR). The term 'ULAR' is applied if the rectal dissection proceeds below the pelvic floor or the rectum is excised completely.

This change in surgical practice has been the consequence of several factors. First, distal intramural spread of cancer used to be a major consideration when planning curative resection and early studies suggested that the distal clearance margin should be at least 5 cm[3–5]. However, more recent studies suggest that distal intramural spread rarely exceeds 1 cm[6–9], and that cases where spread exceeds 1 cm are usually associated with advanced disease with multiple lymph node metastases[10,11]. Distal intramural spread may carry little prognostic significance in determining local recurrence of rectal cancer; overall prognosis may, possibly, be a function of incurable disease at presentation[12,13]. The necessity of total mesorectal excision for these low rectal cancers is now widely accepted[14,15]. Second, the development of stapling devices has enabled anastomoses to be constructed easily within the depths of the pelvis[16–18]. Third, following low anterior resection with total mesorectal excision local recurrence rates have not increased. Local recurrence is not significantly different to that following APR of the rectum[19–21]. Fourth, there is a lower morbidity and complication rate following low anterior resection than that following APR[22,23]. Finally, several studies have demonstrated no increased perioperative or postoperative mortality rate associated with anterior resection compared to that of APR[22–25]. Thus, for carcinoma of the middle and lower third of the rectum, a sphincter-saving operation has become the procedure of choice[26–29].

Functional outcome following ultra-low anterior resection

The major advantage of ULAR compared with APR is the avoidance of a colostomy. This is assumed to be more acceptable to patients and to result in a better quality of life[30]. Certainly it avoids the high psychological morbidity associated with a permanent abdominal stoma[31–33]. A consequence of rectal excision, however, is a greatly reduced reservoir capacity and an alteration in pelvic physiology following reconstruction with a straight coloanal anastomosis. The functional outcome of this is that 5–60 per cent of patients experience disorders of continence, ranging from the inadvertent and uncontrolled passage of flatus to frank faecal incontinence[34–42].

Maintenance of continence depends on a complex neurophysiological integration of the rectum with the anal canal. Within the anal canal the internal anal sphincter (IAS) is thought to be one of the major determinants of the maintenance of continence. The IAS exists in a state of tonic contraction[43], providing the main contribution to the resting pressure which may be measured within the anal canal[44]. It is able to relax in a reflex coordinated manner in response to rectal distension and this is considered to be the physiological basis for the rectoanal inhibitory reflex (RAIR)[45]. As intrarectal pressure increases, there is a transient decrease in pressure in the

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upper part of the anal canal, therefore reducing the pressure gradient and allowing rectal content to come into contact with the richly innervated mucosa (the so-called anal transitional zone). This process, known as sampling, is thought to be the basis of distinguishing whether there is faeces or flatus in the anal canal, permitting appropriate action as socially convenient.

It was initially assumed that continence would be maintained provided the IAS and pelvic floor skeletal musculature remained intact[46,47]. However, the clinical outcome following ULAR is rather different, with patients often suffering increased bowel frequency, urgency of defaecation and minor faecal leakage (anterior resection syndrome)[39,48–50]. So what are the underlying physiological abnormalities following ULAR and how do they explain this functional outcome? Several studies have demonstrated a significant reduction in anal canal mean resting pressure (MRP)[50–52] after anterior resection, although this finding is by no means universal[35,40,53]. Such a fall in MRP has been ascribed to the dilatation of the IAS produced by the stapling gun used for the anastomosis and, interestingly, IAS damage can be detected by endoanal ultrasonography after insertion of the stapler into the rectal remnant[54]. A similar fall in MRP is encountered after transanal endoscopic microsurgery in which the operating sigmoidoscope (external diameter 4 cm) is the cause of anal dilatation[55–57]. Another possible explanation for the fall in MRP after ULAR is damage to the nerve supply of the IAS. The IAS has a dual autonomic innervation, receiving a sympathetic contribution from L1/L2 via the hypogastric nerves and a parasympathetic contribution via the pelvic nerves[58,59]. To investigate the cause of a reduced MRP, Horgan *et al.*[52] performed intraoperative manometric studies in patients undergoing anterior resection for rectal cancer. Following inferior mesenteric artery ligation, there was no change in anal canal MRP. By contrast, following insertion of the stapling device there was a reduction in anal canal MRP. While passage of the stapling device is an unavoidable aspect of ULAR, pelvic nerve damage is a surgeon-dependent variable and may be one area that could be improved[51].

Studies examining the effect of low anterior resection on anal canal maximum squeeze pressure (MSP) from a voluntary effort have produced conflicting results with both a decrease[51] and no significant change[35,39] reported. The external anal sphincter is innervated by the pudendal nerves and it is unlikely that surgical damage to this innervation is the explanation for any decrease in pressure. Surgical trauma to the pelvic floor may, however, be a contributory factor.

The presence or absence of the RAIR continues to be a source of much debate. Based on its mechanism of action, it is easy to understand why many researchers feel this reflex to be of such importance. In a prospective study of ULAR with anorectal physiological evaluation 3 months later, Jehle *et al.*[51] found the reflex was abolished in all 55 patients. Pedersen *et al.*[35] reported that two of 12 patients had a positive RAIR after surgery, although they also noted that seven of the 12 had no RAIR before operation. By contrast, Lewis *et al.*[39] found in patients studied at a median of 13 (range 4–100) months following anterior resection for rectal cancer, that all 34 had a RAIR present. Similarly, and from the same institution, Miller *et al.*[41] detected a positive RAIR in all 30 patients examined at a median of 11 (range 1–96) months after anterior resection. One possible explanation for these differing findings is that of continuing physiological adaptation of the 'neorectum'; this seems likely when one examines the time-scale of these studies. RAIR is more likely to be present as time from operation increases, a reflection of the re-establishment of traumatized neural pathways.

Perhaps the most illuminating recent studies examining the reasons for poor clinical outcome after anterior resection have been those that have directly compared patients with a good result with those with a poor result. In one such study, 19 of 30 patients were deemed to have a poor functional outcome[41]. The sensory threshold of the anal canal mucosa was greater in the upper anal canal (i.e. less sensitive) in those with a poor outcome. Distension of the neorectum resulted in the virtual abolition of the pressure gradient between the upper and lower part of the anal sphincter, such that neorectal pressure exceeded anal canal pressure, the result being an episode of incontinence. In another study, 44 (60 per cent) of 73 patients had disturbance of bowel function following anterior resection[40]. Physiological evaluation revealed that variables such as MRP and MSP were no different between the two patient groups. However, stressing the sphincter mechanism by rectal distension demonstrated differing responses between the groups. In those with a poor outcome, maximum sphincter inhibition occurred at lower distension volumes and, consequently, rectal pressure was greater than at any point along the anal canal. The pressure differential that is noted in the sampling reflex appeared to be lost in patients with a poor outcome. The volume of neorectal distension necessary to elicit such profound sphincteric inhibition was found to correlate with the degree of clinical dysfunction.

The influence of the length of residual rectal stump continues to be a source of debate[51] although most authors agree that it plays a role in determining functional outcome following ULAR[34,36,39,40,49,60]. Jehle *et al.*[51] found that length of rectal stump did not influence outcome in 55 patients when examined 3 months after operation. However, this physiological evaluation was made early in the postoperative period, at a time which is considered by many to be the adaptation phase[61].

Many patients suffer from varying degrees of faecal incontinence. The mechanism underlying this dysfunction is clearly complex, but it probably involves an interplay of poor IAS function secondary to the trauma of pelvic dissection and anal dilatation. Coupled to this is reduced compliance, i.e. diminished capacity for receptive relaxation. The rationale for the creation of a colonic pouch appears attractive. Not only may it increase reservoir capacity, it may also act as a 'pressure sump'[41], in which the high intraluminal pressures generated within the relatively non-compliant colon, are dissipated before reaching the anal canal and overcoming the sphincter mechanism.

Colonic J pouch

The creation of a reservoir to aid bowel function was initially used, in the form of an ileal pouch reservoir, after total colectomy[62,63]. The colon pouch was first reported in 1986, simultaneously in this Journal by Lazorthes *et al.*[64] from Toulouse and Parc *et al.*[65] from Paris. Lazorthes *et al.* described a series of 65 patients, 45 of whom had a straight coloanal anastomosis following ULAR. In the remaining 20 a colonic J pouch was fashioned, a 6-cm pouch in 14 and a 12-cm pouch in six. The most dramatic finding was a significantly reduced bowel frequency in patients with a colonic reservoir compared with those with a straight anastomosis. Physiological evaluation suggested that threshold volume (i.e. degree of rectal distension to elicit first sensation) and maximum tolerable volume were significantly greater in patients with a colon pouch than in those with a straight coloanal anastomosis. They also found an inverse relationship between bowel frequency and maximum tolerable volume of the neorectum. Follow-up after 1 year revealed that 86 per cent of patients with a colon pouch had a bowel frequency of less than 3 per day, compared with only 33 per cent of patients with a straight anastomosis[64]. The series from Parc *et al.*[65] using an 8-cm colon pouch, was equally impressive in restoring bowel function and continence. This series, however, contained the first suggestion of a potential drawback of the colonic reservoir, namely inadequate evacuation. Twenty-five per cent of patients required suppositories on alternative days to help evacuation of the colon pouch[66].

In a similar study of colon pouch *versus* straight coloanal anastomosis following ULAR, Nicholls *et al.*[67] found that ten of 13 and six of nine patients respectively had perfect continence at a median of 7 (range 3–15) months after restoration of pouch function by closure of the defunctioning stoma. Frequency of defaecation was significantly less in those with a colon pouch. Although only one of 13 patients with a pouch in this series required suppositories to aid evacuation, videoproctography suggested incomplete evacuation in three of nine studies by this technique. Kusunoka *et al.*[68] commenced a randomized trial to examine functional outcome of ULAR with or without a colonic pouch but abandoned it before completion because of the apparent superior functional outcome in those with a colon pouch and pouch–anal anastomosis.

How does it work?

In simplistic terms, it is attractive to conceptualize the colon pouch as a neorectum, taking over the complex reservoir function previously performed by the natural rectum. However, physiological assessment suggests that the situation is more complex. Anal canal and MSP are no different before and after operation[69]; nor are they different between patients having a colon pouch or a straight coloanal anastomosis[67,68,70]. A comparison of high anterior resection and low anterior resection with a colon pouch showed no differences in MRP or MSP[71]. While these results suggest that pouch construction is unlikely to result in *impaired* sphincteric function, they also suggest that the improved functional outcome associated with a colon pouch is unlikely to be a consequence of *improved* sphincter function. Interestingly, physiological data from the earliest reports suggested that there was a greater threshold volume and maximum tolerable volume within the colon pouch[64]. These findings have been verified by others[67–69], although work from this unit, within the context of a prospective randomized trial, failed to confirm such findings[70]. Maximum tolerable volume appeared inversely proportional to bowel frequency in several studies, suggesting that the colon pouch may function as a reservoir which both increases capacitance and, possibly, improves compliance, thereby mimicking the rectal property of receptive relaxation. This allows the pouch to distend with faecal contents before intraluminal pressure increases and the desire to defaecate intervenes.

RAIR recovers in 30–100 per cent of patients with a colon pouch[64,67–69], suggesting a re-establishment of the neurogenic pathways necessary for this reflex and, importantly, a coordination of neurogenic and myogenic activity between the pouch and the anal canal. Ambulatory manometry has been used to study 12 patients with a colon pouch (four with minor soiling); in those with a continence disorder there was a much lower pressure gradient between the pouch and the anal canal. However, for the remaining patients, anorectal pressure gradients were similar to those of a group of controls[72]. More interestingly, however, was the demonstration of sampling episodes between flatus and faeces. The importance of this study is its demonstration of the re-establishment of coordinated sensorimotor activity between the colon pouch and the anal canal. In a comparison of functional outcome in patients having high anterior resection (i.e. with a remnant rectum) and those having ULAR with a colon pouch, Ramirez *et al.*[71] found no statistical differences between the two groups in terms of manometric data and functional outcome. They therefore concluded that the colon pouch was behaving as a neorectum.

The possibility of a humorally-mediated mechanism of pouch function has been investigated by measuring levels of peptide YY and enteroglucagon in patients having colon pouches. Peptide YY is a potent inhibitor of intestinal transit and stimulates absorption[73–75]; it is secreted largely in the distal colon and rectum[76]. Enteroglucagon appears to be a trophic stimulant to the gut mucosa[77]. In a randomized trial of patients with a colon pouch *versus* straight anastomosis, Hallböök *et al.*[78] failed to detect any difference in plasma concentration of either peptide at any time period after surgery between the two groups. They concluded that neither of these humoral agents was a factor in determining pouch function. Based on the data presently available, one can only surmise that pouch function is a complex physiological process involving the integration of sensory, motor (and possibly humoral) responses between the pouch and the anal canal.

How big should the pouch be?

Pouch size remains a source of some debate. Initial reports described pouches of 8 cm[65,66], 9 cm[68] and 10 cm[67], with Lazorthes *et al.*[64] using pouch sizes of 6 cm and 12 cm. One of the major drawbacks of a colon pouch is evacuation difficulty. In one early series from Paris, 25 per cent of 162 patients had to use suppositories or enemas to achieve evacuation and avoid impaction with overflow[66]. This assessment was at 1 year following closure of colostomy and initiation of pouch function. Similar problems have been described by other workers: 48 per cent of patients with a 9-cm pouch by Pelissier *et al.*[79], 37 per cent of patients with a 9-cm pouch by Mortensen *et al.*[69] and three of nine patients with a 10-cm pouch by Nicholls *et al.*[67].

Banerjee and Parc have attempted to solve the problem of ascertaining optimum pouch size by using a mathematical model[80]. This was based on the assumption that pouch volume is a function of the length of colon used and colon diameter. The conclusion was an optimum pouch size of 8–10 cm. Unfortunately, this simplistic approach is fundamentally flawed as it fails to account for the physiological characteristics of the neorectum, in particular, motility. In a clinical study to determine optimum size, 40 patients were randomized to have either a 5-cm or 10-cm pouch after ULAR[81]. Although some physiological variables (threshold volume, maximum tolerated volume and compliance) were less in the 5-cm group, the functional outcome was essentially identical between the two groups. Both groups underwent a balloon expulsion test to assess evacuatory function. This was performed by inserting a balloon into the pouch and filling it with 500 ml saline; the patient was then instructed to attempt to expel the balloon in the sitting position and the volume expelled was measured. The expelled volume in the 5-cm pouch groups was significantly greater than that in the 10-cm group a mean(s.d.) of 430(32) *versus* 279(65) ml ($P<0{\cdot}001$, Student's t test). The authors concluded that, in terms of functional outcome, a 5-cm pouch was as good as a 10-cm pouch, but without the evacuatory problems of the larger construction[81]. This finding is of interest as it confirms that pouch function is not a simple mathematical derivative of reservoir capacity. It also gives credence to the contention that pouch function may in some way be related to altered motility, possibly to reversed peristaltic movements in the J pouch reducing transit time[70]. It is likely that the future trend will be to a small pouch size, probably 5–7 cm in length. A pouch size of 8–10 cm is too long if evacuatory problems are to be avoided.

Which part of the colon should be used?

Both sigmoid[65,66] and descending[70,82] colon have been used to construct a pouch. The choice of which to use has not been the focus of any particular study and so it is difficult to be objective. Oncological and operative factors may largely determine which part of the colon is most suitable. In a Western society with an ageing population in whom diverticular disease of the sigmoid may be quite prominent, it seems unwise to choose this part of the colon from which to construct a pouch. Similarly, in a relatively young person with a healthy colon, it may appear inappropriate to excise more colonic tissue than is necessary (once oncological principles have been satisfied). If there is concern about adequate lymphatic clearance when using the sigmoid, it is reassuring to note that after a comprehensive assessment of the lymphatic spread of rectal cancer Hida *et al.*[83] found node positivity to be less than 1 per cent at this level. These authors felt justified in using the sigmoid colon for pouch construction. However, it is the present authors' belief that routine excision of the sigmoid colon is preferable, using the descending colon after full splenic mobilization for pouch construction; these are key factors in optimizing functional outcome[84].

Does pouch construction affect anastomotic leak rate?

The concept of a colonic end-to-side anastomosis in the pelvis is not new. As far back as 1950 Baker[85] reported, in a retrospective study, a leak rate of 23 per cent for conventional end-to-end colorectal anastomosis and only 4 per cent with a side-to-end anastomosis. It is of interest to note that in the colon pouch series from Berger *et al.*[66] pelvic sepsis/anastomotic leakage occurred in only five patients (3 per cent). Similarly, in another small series of 23 patients with a colon pouch there were no documented leaks[86]. This compares favourably with leak rates observed following stapled low coloanal anastomoses which range from 5 to 15 per cent[87–91].

Successful bowel anastomoses are those without tension and with a good blood supply. It is not possible to investigate formally the effect of tension within an anastomosis in the clinical setting, but it is possible to investigate blood flow. One study investigated colonic blood flow using laser Doppler flowmetry within a randomized control trial of pouch *versus* straight anastomosis[92]. Measurements of blood flow were made at the bowel end (i.e. after mobilization and transection) and at a point 8 cm proximal to the end (i.e. the site of proposed colon pouch–anal anastomosis). Blood flow at the end of the bowel was significantly lower after mobilization of the colon, whereas at the bowel wall 8 cm proximally there was no significant change. It was concluded that the blood supply to a colon pouch–anal anastomosis was better than that to a straight colorectal or coloanal anastomosis. This may, in part, explain the apparently lower anastomotic leak rates noted in colon pouch–anal anastomoses.

Functional outcome

From the earliest reports it was apparent that the functional outcome using a colon pouch–anal anastomosis was superior to that of a straight coloanal anastomosis; this was evident well within the first year after operation[64–66]. Although coloanal anastomoses may be associated with a satisfactory outcome in some patients[93], for others poor sphincteric function coupled with urgency and frequency of defaecation prove crippling. Not surprisingly, the functional improvement following colon pouch–anal anastomosis after ULAR described in early reports was enthusiastically received. Lazorthes *et al.*[64] found that after 1 year, 86 per cent of patients with a colon pouch had a bowel frequency of less than 3 stools per day, compared with only 33 per cent of patients with a straight coloanal anastomosis. The results were even more dramatic in the series reported by Parc *et al.*[65] who described a mean of 1-6 bowel movements per day after 1 month and 1·1 per day after 3 months in a group of 31 patients with a colon pouch. The only potential disadvantage of the pouch was faecal retention secondary to poor evacuation. This was observed in 25 per cent of patients in one of the early series; these patients required suppositories on alternate days[66]. The functional outcome of colon pouch–anal anastomosis in these early and subsequent series are presented in *Table 1*. What is striking is that all studies confirm a reduction in bowel frequency and a reduced incidence of urgency from the use of a colon pouch. More recently, three prospective randomized controlled trials have been performed to compare directly physiological and functional outcome following ULAR in patients with or without a colon pouch (*Table 2*). Again the colon pouch emerges as the superior option. It improves functional outcome, with reduced bowel frequency, reduced need for antidiarrhoeal medication and reduced incidence of urgency.

Conclusion

It is now beyond doubt after ULAR that a colon pouch proximal to the anastomosis produces superior functional results compared with those of a straight coloanal anastomosis. Improvement is apparent from the early postoperative period when function may be at its most critical. This is especially important in the elderly who often have impaired sphincter function, which may be easily

Table 1 Functional outcome following colon pouch–anal anastomosis

Reference	Year	No. of patients	Bowel frequency per 24 h	Urgency	Incontinence	Evacuation problems	Enemas required
Lazorthes *et al.*[64]	1986	20	1–2 (12 of 20) > 3 (8 of 20)	2	4	0	2
Parc *et al.*[65]	1986	31	1·1	0	0	8	8
Nakahara *et al.*[94]	1988	8	2·3(1·4)*	1	3	1	2
Nicholls *et al.*[67]	1988	13	1·4 (0·5–2)†	1	3	1	1
Kussunoka *et al.*[68]	1991	28	2	—	2	—	—
Guillemot *et al.*[95]	1991	18	2·8(1·6)§	—		5 of 14§	—
			4·2(1)¶		4	4 of 4¶	
Pelissier *et al.*[79]	1992	33	1·5(0·8)*	1	—	—	—
Cohen[86]	1993	23	2 (1–4)†	5	4	—	—
Mortensen *et al.*[69]	1995	23	2·1 (1–4)‡	5	4	7	6
Ortiz *et al.*[96]	1995	15	1–3 (10 of 15) > 4 (5 of 15)	6	8	—	—
Ramirez *et al.*[71]	1996	10	2·2(1·1)*	2	2	3	—
Romanos *et al.*[72]	1996	12	3 (1–6)†	6	4	7	
Kusunoki[97]	1997	38	2·0(1·2)*	1	7	27	—

Values are *mean(s.d.), †median (range) or ‡mean (range). §Continent patients; ¶incontinent patients

Table 2 Results of randomized trials to compare outcome in patients with a colon pouch and those with a straight anastomosis

	Seow-Choen and Goh 1995[82]			Hallböök *et al.* 1996[98]			Ho *et al.* 1996[70]		
	Pouch	Straight	*P*‡	Straight	*P*‡	Pouch	Straight	*P*‡	
No. of patients	19	20		43	50		17	16	
Bowel frequency	2 (0·5–4)*	2 (0·5–10)*	< 0·05	2 (1·3–2·3)†	3·5 (2·4–4·5)†	< 0·001	3 (2–7)*	6 (3–7)*	0·02
Antidiarrhoeal medication	0	9	< 0·008	1	19	< 0·001	5	6	n.s.
Urgency < 15 min	2	4	n.s.	2‡	15‡	< 0·001	5	1	n.s.
Normal continence	19	14	< 0·01	2 (0–5·3)†§	5 (2–9)†§	0·0019	16	15	n.s.
Pads required	1	3	n.s.	—	—	—	1	1	n.s.
Incomplete evacuation	—	—	—	5	7	n.s.	10	3	0·02
Enemas/suppositories required	0	7	n.s.	4	0	0·046	—	—	—

Values are *median (range) or †median (interquartile range). ‡Urgency > 30 min; §continence score 0–8. n.s., Not significant

overwhelmed by the urgency and frequency associated with a coloanal anastomosis. For those with limited life expectancy it is also desirable to achieve optimum results as quickly as possible. At a time when the indications for APR appear to be reduced or even non-existent for cancer of the lower third of the rectum[99,100], the superiority of the colon pouch over straight coloanal anastomosis should make pouch construction more widespread in this situation.

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Review

Quality of life after treatment for rectal cancer

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Background The studies on patient-reported symptoms and quality of life following the treatment of rectal cancer were evaluated; guidelines for future quality of life studies in this field are proposed.
Methods Relevant papers in the English language were identified via Medline from January 1970 to November 1997, supplemented by a manual search for similar articles.
Results Patients suffer various short- and long-term complications after treatment of rectal cancer, although the reported prevalence of such problems varies from study to study. Recent prospective studies have shown that, despite these problems, global quality of life scores as measured by generic questionnaires improve after surgery.
Conclusion The methodological shortcomings of previous work must be rectified if quality of life studies are to have relevance in patient management.

Rectal cancer is a tumour of major importance, representing 40 per cent of colorectal cancers. It is a disease which mainly affects the elderly, and has its highest incidence in Western Europe and North America. The reported incidence in 1991 for England and Wales was 20 per 100 000, with a mortality rate of 11·1 per 100 000 for that same year[1,2].

Surgery is the definitive form of treatment for rectal cancer; by resecting the tumour the surgeon not only aims to cure the patient but to relieve distressing symptoms[3]. Unfortunately, patients must suffer adverse consequences from such surgery. The operative dissection of the rectum may damage the pelvic autonomic nerves, disturbing bladder and sexual function[4,5]. The construction of a permanent colostomy following an abdominoperineal resection may be associated with clinically significant psychological problems[6]. With advances in knowledge of tumour biology and improvements in surgical instruments and techniques, survival and tumour recurrence rates are similar after anterior resection and abdominoperineal resection[5,7], resulting in an increasing number of restorative procedures being performed. Although avoidance of a permanent stoma is generally regarded as a favourable outcome measure, patients undergoing sphincter-saving surgery may develop a number of unpleasant symptoms, typically faecal soiling and urgency, especially with low anastomoses[8–19]. The provision of a colonic pouch reservoir may reduce such problems, but difficulties with evacuation of the neorectum have been described[20].

It is evident that the consequences of rectal surgery have an important bearing on a patient's quality of life. Although differences in definition exist[21,22], 'quality of life' may be regarded as representing an individual's ability to carry out daily activities, as well as satisfaction with personal performance and with the balance between disease control and adverse effects of treatment[22]. Quality of life is assessed by using specifically designed questionnaires which test the various components of physical, social and psychological well-being[21–23].

The aim of this review is to evaluate the studies of one or more components of quality of life and to outline proposals for future quality of life studies in rectal cancer surgery. Studies on the effect of radiotherapy and chemotherapy for advanced disease on quality of life are also discussed.

Study design

A total of 54 papers published in the English language on aspects of quality of life in rectal cancer surgery was analysed. Forty were cross-sectional or retrospective studies and 14 were prospective studies. In only three studies was global quality of life formally measured using a well researched questionnaire[24–26]. The others investigated only isolated symptoms using, in most cases, unresearched and unvalidated questionnaires. Sample sizes in these studies varied from five to 265, with the majority involving groups of less than 25 patients; follow-up was from 1 month to 30 years after surgery. Some reports did not distinguish between short-term and long-term complications.

One study assessed quality of life in patients with colorectal cancer who were having radiotherapy[27]; another six assessed quality of life during chemotherapy and radiotherapy[28–33]. Well validated questionnaires were used in only three of these studies.

Statistical analysis of results was used in most reports; the commonest test measuring significance was χ^2 analysis.

Social well-being

Social problems encountered by patients after rectal cancer surgery were described in eight cross-sectional studies. Devlin *et al.*[34] reported in 1971 that 51 per cent of patients over 65 years old who had a colostomy felt socially isolated, in contrast to 19 per cent of younger patients with a stoma. Women felt more socially isolated than men. Wirsching *et al.*[35] in 1975 examined a group of 214 patients who had a permanent colostomy and a group of 110 who had restorative surgery. There was significantly

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reduced social contact in the colostomy group. Similarly, MacDonald and Anderson[36] in 1985 noted that those with a colostomy tended to participate less in social activities than those without a stoma; their interests in outdoor pursuits were significantly less. A statistically significant difference was also noted by Williams and Johnston[8] who compared the leisure pursuits of patients with a colostomy (50 per cent decrease) and those without (18 per cent decrease). Despite all of this, Frigell *et al.*[10] in 1990 were unable to detect any difference in the rate of decreased social activities when they compared patients with an anterior resection with those with an abdominoperineal resection (19 *versus* 17 per cent). Indeed, 74 per cent of those with an anterior resection avoided public societies compared with 59 per cent of those with abdominoperineal resection.

In 1984 MacDonald and Anderson[37] found a worsening partner-relationship in 29 per cent of patients with a colostomy compared with 14 per cent of those who had a sphincter-saving resection. This result was statistically significant. On the other hand, La Monica *et al.*[38] in 1985 did not find any such difference. In a study by von Smitten *et al.*[39] in 1986, only one patient reported severe impairment of his social life due to a colostomy; 13 of 54 patients reported only minor impairment.

Social life may deteriorate after surgery for rectal cancer, although results are contradictory. A colostomy may bring a fear of being a nuisance to other people, mainly because of odour, and there may be embarrassment about the presence of a stoma[10,35,37,39]. However, similar problems beset those who are incontinent of flatus and/or faeces following a restorative rectal resection[10].

Psychological well-being

Psychological aspects of quality of life have been researched in four cross-sectional studies. Devlin *et al.* in 1971[34] found that 23 per cent of 83 patients suffered from a severe form of psychological disturbance after abdominoperineal resection, compared with one of 37 patients who had a sphincter-saving operation. These data were not tested statistically. Williams and Johnston[8] in 1983 reported a 32 per cent prevalence of depression following an abdominoperineal resection, compared with a 10 per cent prevalence after anterior resection. These researchers used the 'Leeds Self-Assessment of Depression and Anxiety Scales' and their results were statistically significant. Sixty-six per cent of their patients were distressed after abdominoperineal resection because of an alteration in body image caused by the colostomy; only 5 per cent expressed concern about physical appearance after a sphincter-saving procedure.

In 1975 Wirsching *et al.*[35] understood that a colostomy was associated with a significant degree of depression, hopelessness, loneliness and suicidal thoughts. They used the Heidelberg Colostomy Questionnaire in their study which covered mainly social and psychological function in patients with a stoma. The patients after abdominoperineal resection studied by MacDonald and Anderson[37] in 1984 were found to have a statistically significant higher incidence of low self esteem and feelings of stigma than those who had undergone a sphincter-saving resection. In agreement with the observations made by Williams and Johnston[8], these authors stated that those with a colostomy were more concerned about their appearance than those with an anterior resection. However, the incidence of anxiety in the two operated groups was similar, as was the incidence of depression.

These studies show a high prevalence of psychological problems in patients operated for rectal carcinoma, even though the instruments used in most cases may not be psychometrically reliable. Patients with colostomies tend to suffer most[8,34,35,37,40]. The degree of psychological distress before surgery was not recorded in any of these studies.

Physical well-being

There were 49 studies which dealt with the effect of rectal cancer surgery on physical well-being. Symptoms investigated pertained mainly to sexual, urological and defaecatory functions.

A spectrum of sexual problems may arise in men[8,34,35,38,41–59]. These typically involve erectile and ejaculatory dysfunction (*Table 1*), although other symptoms, such as a loss of desire, diminished sexual activity and anorgasmia, may occur. Sexual problems in women have not been as extensively researched. The problems described are fewer, and are mainly cessation of intercourse, anorgasmia and dyspareunia[34,35,50,60]. Both men and women who have had an abdominoperineal resection or a low anterior resection tend to have a higher prevalence of sexual problems than those with a high anterior resection[34,41–43,50,53]. There is also a high prevalence in the elderly[46,56]; male sexual problems appear generally to increase with age, although not all authors agree on this[48].

Urological difficulty following surgery has also been described[36,46,48,50,51,58,61–64], especially incontinence, retention and dysuria. The relevant studies are summarized in *Table 2*. As with sexual problems, abdominoperineal resection is associated with more urological problems than anterior resection[36,48,50], but results in some studies are not statistically significant.

Sexual and urological symptoms usually occur secondary to damage to the pelvic autonomic nerves and pelvic floor sustained during dissection of the rectum[4,5]. Operative techniques such as total mesorectal excision with autonomic nerve preservation, in which the pelvic nerves are carefully identified during surgery, may result in less sexual and urinary dysfunction[5,58,59,65].

A number of studies have been carried out to assess bowel and sphincter function after surgery for rectal cancer (*Table 3*). The common symptoms are frequency of bowel motion, urgency, and faecal leakage or incontinence[8–15,17–20,66–70]. Some authors also report on the prevalence of diarrhoea, constipation and flatus[8,10,34,36]. Many relevant issues emerge from such work. Bowel function, which may be erratic before surgery because of the tumour, may not improve after operation[18]. According to Williams and Johnston[8], the frequency of bowel motions is usually greater after abdominoperineal resection than after anterior resection, but Frigell *et al.*[10] disagree. Patients with a colostomy tend to have more problems with flatus and foul odour than other patients[8,36], but the prevalence of diarrhoea is similar in both groups[36].

Bowel function after sphincter-saving resection depends on several factors. The level of anastomosis may be relevant. A low colorectal or coloanal anastomosis is associated with a higher frequency of defaecation and a higher prevalence of faecal leakage and incontinence than a high colorectal anastomosis[11,17,49,65], although not all studies agree on this[10,16]. Defaecatory problems may also arise from surgical trauma to the anal sphincter and its innervation[16]. Anorectal physiological assessment shows that the threshold reservoir volume and maximum tolerable volume are significantly lower after a low colorectal or coloanal anastomosis than after a higher anastomosis[17]. The maximum resting pressure and, in some cases, the maximum squeeze pressure, which measure the internal and external anal sphincters respectively, are lowered after operation[11,13,17,71,72]. Any improvement of bowel function in the long term is usually reflected by an improvement in the physiological status of the anoneorectum[13,17,71,72]. In patients who experience poor function, however, the anal sphincter pressures and the rectoanal inhibitory reflex remain abnormal[15,65,71,72]. The construction of a colonic J pouch may improve bowel function in those who undergo a low anterior resection[14,15] as the threshold and maximum tolerable volumes of the neorectum increase[66,67]. However, difficulties in evacuation of the pouch may occur[20], especially with pouches of a larger volume[73], requiring the use of a suppository or an enema. A number of patients may remain plagued with defaecatory problems, and may require revisionary surgery[19].

Formal quality of life studies in rectal cancer surgery

To date there are only three reports in the English language literature which describe formally measured quality of life in all its dimensions after surgery for rectal cancer[24–26]. All three studies used the Nottingham Health Profile, a questionnaire which measures the subjective

Table 1 Sexual problems in men after surgery for rectal cancer

Reference	Year	Operation	Total no. of patients	No. with impotence	No. with ejaculatory dysfunction	Comments
Goligher[41]	1951	APR	81	23 (28)	49 (60)	
		AR	14	2 (14)	7 (50)	
Devlin *et al.*[34]	1971	APR	55	29 (53)		
		AR	15	2 (13)		
Wirsching *et al.*[35]	1975	APR	17	3 (18)	10 (59)	
Weinstein and Roberts[42]	1977	APR	12	12 (100)		Mean age 67 years
		LAR	10	8 (80)		Mean age 66 years
Fazio *et al.*[43]	1980	APR	6	1 (17)	2 (33)	
		LAR	7	1 (14)	2 (29)	
Williams and Slack[44]	1980	LAR	5	0 (0)	0 (0)	Before operation
		LAR	5	0 (0)	2 (40)	After operation
Yeager and Van Heerden[45]	1980	APR	20	3 (15)	5 (25)	
de Bernardinis *et al.*[47]	1981	APR	31	16 (52)		
Danzi *et al.*[46]	1983	APR	26	7 (27)	14 (54)	
		LAR	30	7 (23)		
Balslev and Harling[48]	1983	APR	93	17 (18)	30 (32)	
		LAR	17	0 (0)	6 (35)	
McDonald and Heald[49]	1983	AR (> 10 cm)*	7	0 (0)	0 (0)	
		AR (5–10 cm)*	8	2 (25)	2 (25)	
		AR (< 5 cm)*	6	2 (33)	3 (50)	
Williams and Johnston[8]	1983	APR	17	8 (47)	12 (71)	
		SSR	20	4 (20)	7 (35)	
La Monica *et al.*[38]	1985	APR	20	10 (50)	14 (70)	
		LAR	20	4 (20)	8 (40)	
		HAR	20	1 (5)	5 (25)	
Fegiz *et al.*[50]	1986	APR	30	18 (60)	29 (97)	
		LAR	31	12 (39)	18 (59)	Manual anastomosis
		LAR	42	24 (57)	30 (71)	Stapled anastomosis
Kinn and Ohman[51]	1986	APR + LAR	10	3 (30)	8 (80)	
Cirino *et al.*[52]	1987	APR	28	7 (25)	12 (43)	
Santangelo *et al.*[53]	1987	APR	9	4 (44)	6 (67)	All < 60 years
		LAR	12	4 (33)	7 (58)	
		HAR	4	0 (0)	1 (25)	
Zenico *et al.*[54]	1989	APR	15	1 (7)	8 (53)	Mean age 49 years
Hojo *et al.*[55]	1991	AR + APR	10	2 (20)	4 (40)	After complete ANP
		AR + APR	18	14 (78)	18 (100)	After partial ANP
		AR + APR	11	11 (100)	11 (100)	No ANP
Enker[56]	1992	LAR	24	1 (4)		< 60 years
		LAR	14	4 (29)		> 60 years
Filiberti *et al.*[57]	1994	LAR	21	2 (10)	17 (81)	
Havenga *et al.*[58]	1996	LAR	56	8 (14)	16 (29)	After ANP and TME
		APR	21	7 (33)	7 (33)	
Masui *et al.*[59]	1996	AR + APR	134	16 (12)	44 (33)	After ANP

Values in parentheses are percentages. *Level of anastomosis from anal verge. APR, abdominoperineal resection; AR, anterior resection; LAR, low anterior resection; SSR, sphincter-saving resection; HAR, high anterior resection; ANP, autonomic nerve preservation; TME, total mesorectal excision

Table 2 Urinary problems after surgery for rectal cancer

Reference	Year	Operation	Main symptoms	Total no. of patients	No. with symptoms
Kirkegaard *et al.*[61]	1981	LAR	Urgency, frequency, poor stream	19	5 (26)
Neal *et al.*[62]	1981	LAR (preop.)	Nocturia, poor stream, incontinence	27	9 (33)
		LAR (postop.)		27	16 (59)
Balslev and Harling[48]	1983	APR	Dysuria, incontinence	31	29 (93)
		LAR		17	0 (0)
Zanolla *et al.*[63]	1984	APR	Retention of urine	44	23 (52)
MacDonald and Anderson[36]	1985	APR	Dysuria, incontinence	265	64 (24)
		AR		155	19 (12)
Fegiz *et al.*[50]	1986	APR	Retention, hesitancy	61	12 (20)
		LAR		66	9 (14)
Kinn and Ohman[51]	1986	APR + AR	Difficulty in voiding	22	7 (32)
Zanolla *et al.*[64]	1988	AR	Hesitancy, dysuria, poor stream	21	13 (62)
Havenga *et al.*[58]	1996	APR + LAR (M)	Frequency, urgency, dysuria	82	12 (15)
		APR + LAR (W)		54	20 (37)

Values in parentheses are percentages. LAR, low anterior resection; APR, abdominoperineal resection; AR, anterior resection; M, men; W, women

psychological, functional and social impact of disease[74]. Its reliability and validity are proven. In addition, one study[24] used a shortened version of the Health Measurement Questionnaire, while another[25] used a selection of questions from the Rotterdam Symptom Checklist, the latter questionnaire being validated for use in patients with cancer[75].

In a retrospective study by Whynes *et al.*[24] in 1994 of over 400 individuals, no difference was found between the scores of 77 patients with a colostomy and those of patients with a restorative surgical procedure for colorectal cancer. However, the same authors in 1997, in a prospective study of 49 patients[25], noted an improvement in some postoperative scores for all colorectal operations compared with preoperative scores. The main area of improvement was in the emotional reactions dimension.

In 1997 Hallbook *et al.*[26] commented on the general quality of life before and a year after restorative rectal cancer surgery; this occurred as part of a prospective randomized trial comparing a straight and a colonic J pouch anastomosis. The scores improved in both groups after operation; there was no difference in scores between the two groups. So global quality of life, measured by the Nottingham Health Profile, was similar, despite the superiority in bowel function in patients with a J pouch which had been demonstrated in an earlier study[69].

Effect of radiotherapy and chemotherapy

Both preoperative and postoperative adjuvant radiotherapy have been shown recently to decrease the incidence of local recurrence of rectal cancer[76]. A beneficial effect on survival has been demonstrated in one recent study using preoperative radiotherapy[77]. However, a number of short-term and long-term complications of treatment are recognized. In the short term, there is a statistically significant increase in the incidence of perineal wound infection after abdominoperineal resection preceded by radiotherapy[78]. In the long term, both preoperative and postoperative radiotherapy are associated with an increased incidence of venous thromboembolism, arterial disease, fractures of the pelvis and femoral neck, intestinal obstruction, colovesical and colovaginal fistula, and urinary tract infection[79,80]. The effect of preoperative radiotherapy on anorectal function is minimal[81,82], but radiotherapy administered after an anterior resection may have a detrimental effect on sphincter function, rectal capacity and clinical outcome[83]. One study assessed quality of life over the duration of pelvic radiotherapy for colorectal cancer[27]. As measured by the Health Quality of Life Index, quality of life appeared to remain at an acceptable level throughout the treatment.

The toxicity of chemotherapy and its impact on quality of life has been examined in patients with advanced metastatic colorectal disease. Six prospective studies were identified[28–33]. Toxic side-effects include anaemia, neutropenia, diarrhoea, nausea, vomiting, anorexia and alopecia. Glimelius *et al.*[28] reported an overall improvement in quality of life scores in 36 per cent of patients with metastatic colorectal cancer receiving chemotherapy. The same authors had previously reported that patients receiving both methotrexate and 5-fluorouracil (5-FU) had a better quality of life than those receiving 5-FU alone[29]. However, Laufmann *et al.*[30] found no difference in quality of life scores between patients having 5-FU and placebo and those having 5-FU and leucovorin. Seymour *et al.*[31] showed that the addition of interferon to 5-FU and leucovorin was associated with a decreased quality of life; this study used the Rotterdam Symptom Checklist and the Hospital Anxiety and Depression Score.

Two studies have combined quality of life and survival into a single measure in order to compare treatment regimens. In one, hepatic artery infusion of floxuridine for colorectal liver metastases was found to prolong both overall and normal-quality survival, compared with conventional palliative therapy[32]. The Rotterdam Symptom Checklist and the Hospital Anxiety and Depression Score were used in this study. In the other study, Gelber *et al.*[33] combined quality and quantity of life using a Quality-adjusted Time without Symptoms and Toxicity analysis. The time with toxic side-effects of chemotherapy and radiotherapy was subtracted from the overall survival time. Although there was more toxicity associated with combined chemotherapy and radiotherapy than with radiotherapy alone in patients with rectal cancer and lymph node metastases, the time spent free of any symptoms or side-effects was greater in the combination group than in the radiotherapy group. The social and psychological dimensions of quality of life were not assessed and so it is not known which treatment regimen is more beneficial to well-being.

Discussion

After potentially curative surgery for rectal cancer, patients may suffer from a range of problems affecting the physical, social and psychological aspects of their life. Physical problems are related mainly to sexual[8,34,35,38,41–60], urinary[36,46,48,50,51,58,61–64] and bowel[8–20,66–70] function. Men suffer from impotence and ejaculatory difficulties, among others, while women suffer mainly from dyspareunia. Urinary problems include incontinence, retention and dysuria. The prevalence of these symptoms is on the whole greater with an abdominoperineal resection than with an anterior resection, and such symptoms generally increase with age. Most studies report a higher incidence of faecal incontinence and frequency of defaecation after a low anterior resection than after a higher anastomosis. Defaecatory problems have, in general, been improved by the provision of a colonic J pouch. Social[8,10,34–39] and psychological[8,34,35,37] problems are present after both sphincter-saving and sphincter-sacrificing surgery, although such problems may be more prevalent with the latter.

Although such work clearly demonstrates complications, it fails to show how the overall quality of a patient's life is affected as a result of rectal cancer and its

Table 3 Bowel function after surgery for rectal cancer

			< 1 year after operation					> 1 year after operation				
Reference	Year	Operation	Total no.	No. with frequency > 3–4 per 24 h*	Daily stool frequency	Urgency (%)	Faecal leak (%)	Total no.	No. with frequency > 3–4 per 24 h*	Daily stool frequency†	Urgency (%)	Faecal leak (%)
Williams and Johnston[8]	1983	APR						38	21 (55)			66
		SSR						40	14 (35)			15
McDonald and Heald[49]	1983	AR (> 10 cm)§									17	9
		AR (5–10 cm)§									25	25
		AR (< 5 cm)§									52	57
Lazorthes *et al.*[66]	1986	LAR + CPA	20	8 (40)	2·4(1·2)‡	10	20	15	2 (13)	1·7(0·7)‡	7	7
		LAR + CA	42	28 (67)	3·6(1·3)‡	24	33	36	24 (67)	3(1)‡	6	11
Parc *et al.*[20]	1986	LAR + CPA			1·6 (0·5–3)†	0	33					
Nicholls *et al.*[9]	1988	LAR + CPA	13	0 (0)	1·4(0·5–2)†	8	23					
		LAR + CA	15	4 (27)	2·3(1–6·5)†	7	47					
Frigell *et al.*[10]	1990	APR						29	11 (38)			13
		AR (> 12 cm)§						2	1 (50)			
		AR (7–12 cm)§						11	10 (91)			
		AR (0–6 cm)§						18	13 (72)			
		AR (all patients)						31	24 (77)		18	17
Lewis *et al.*[11]	1992	AR (> 12 cm)§								1(1–4)†	0	0
		AR (4–12 cm)§								2(1–4)†	0	18·2
		AR (< 4 cm)§								3(1–10)†	33	67
		LAR + CA								4(2–8)†	46	73
Paty *et al.*[12]	1994	LAR + CA						81	18 (22)	2(0·3–15)†	19	28
Williamson *et al.*[13]	1995	LAR			4(1–9)†	24	53			4(1–7)†	18	29
Seow-Choen and Goh[14]	1995	LAR + CPA	20	7 (35)	2·5(0·5–10)†			19	1 (5)	2(0·5–4)†	11	0
		LAR + CA	20	13 (65)	4(2–20)†			20	6 (30)	2(0·5–10)†	20	30
Miller *et al.*[15]	1995	LAR + CA				30	63					
Ortiz *et al.*[67]	1995	LAR + CPA						15	5 (33)		40	53
		LAR + CA						15	11 (73)		60	67
Mortensen *et al.*[68]	1995	LAR + CPA			2·1(1–4)†	26	21					
Hallbook *et al.*[69]	1996	LAR + CPA			2(1·5–2·5)†					2(1·3–2·3)†		
		LAR + CA			6·4(4·5–8·1)†					3·5(2·4–4·5)†		
Ho *et al.*[70]	1996	LAR + CPA								3(2–7)†	6	6
		LAR + CA								6(3–7)†	31	6
Ikeuchi *et al.*[17]	1996	AR (9–20 cm)§			3·8(0·3)‡	5·3	0			2·1(0·2)‡	0	0
		LAR (5–8 cm)§			6·7(0·5)‡	62	15			3·8(0·3)‡	3	0
		LAR + CA (3–4 cm)§			7·1(0·6)‡	75	30			4·4(0·2)‡	25	10
Ortiz and Armendariz[18]	1996	LAR								2·3(0·5–6)†	40	52
Lazorthes *et al.*[19]	1997	LAR + CPA	18	2 (11)		22	6	13	2 (15)		8	0
		LAR + CA	19	12 (63)		63	26	12	6 (50)		0	0

*Values in parentheses are percentages; †values are median (range) or ‡mean(s.d.). §Level of anastomosis from anal verge. APR, abdominoperineal resection; SSR, sphincter-saving resection; AR, anterior resection; LAR, low anterior resection; CPA, colopouch–anal anastomosis; CA, coloanal anastomosis treatment. Studies that assessed quality of life have so far shown an overall improvement after operation, irrespective of the operation performed[24-26]. Such results are unexpected because patients with a stoma were perceived to have poorer quality of life than other patients with restorative rectal surgery[8,34-37,84]. Adjuvant radiotherapy is associated with a number of complications, but its effect on quality of life must be assessed in more depth[27]. Some chemotherapy regimens for advanced metastatic colorectal cancer are better than others in terms of quality of life, although the methods of measurement of quality of life differ from study to study[28-33].

More work is needed on quality of life and rectal cancer[84]. Prospective studies of sufficiently large numbers of patients should be carried out to assess quality of life before and after operation[21-23,85,86] and, since quality of life changes over time, measurements should be made at various intervals after surgery[21-23,85-87]. Assessment should also be made during adjuvant treatment to evaluate the impact of such treatment on quality of life[88,89]. Current prospective chemotherapeutic trials in rectal cancer are already using quality of life as a serious study end point.

It is well known that a large amount of information on quality of life may be obtained by detailed interview[21-23]. However, this approach is not practical for routine use where a questionnaire that is short and in simple language is needed to allow easy completion. This enhances patient compliance despite repeated administration[21-23,87]. Despite its brevity, such a questionnaire should still ideally cover all aspects of quality of life. It should also have certain properties to make it psychometrically sound, unlike many of the questionnaires that have been used in the studies described in this review. The instrument must be of proven validity, that is it must measure the intended variable and not another. It must be reliable, measuring the variables accurately, and also sensitive, measuring any changes present[21-23,87].

Generic questionnaires, such as the Nottingham Health Profile, are useful and allow the researcher to compare quality of life across whole patient populations[67]. However, they may not be sensitive enough to measure changes in quality of life which may be brought about by different types of surgery or adjuvant treatment. This may have been the case where the Nottingham Health Profile was used in some recent studies[24-26]; in these no treatment difference was found between either an abdominoperineal resection and a restorative colorectal resection, or between a low anterior resection with colopouch anal anastomosis and a low anterior resection with a straight coloanal anastomosis. On the other hand, differences in global quality of life associated with different operations may truly not exist, the benefit of surgery resulting solely from the removal of the tumour, irrespective of the surgical technique used. Questionnaires which have been designed for use in patients with cancer, such as the Rotterdam Symptom Checklist[75] and the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 core questionnaire[90], may be more suitable. In addition, further questionnaires specific to colorectal cancer are necessary. For example, the EORTC group has recently developed a colorectal cancer questionnaire or module (QLQ-CR38), which has been validated in the Netherlands and is being tested in a number of international phase III trials[91].

Doctors have been noted in various studies to be poor assessors of their patients' quality of life[92-94]. It is therefore important that valid measures of quality of life should be constructed, involving the patients themselves, thereby eliminating observer bias and interobserver variation[92].

Conclusion

Quality of life studies in oncology are of increasing importance. Their main aim is to determine the impact of cancer and its treatment on patients' well-being. In addition to traditional endpoints, such as survival and disease recurrence, quality of life assessment is necessary to provide a proper, comprehensive understanding of the outcome of surgery and other forms of treatment. Quality of life studies may also be used to evaluate the quality of care which patients receive, potentially allowing management to be improved and services to be designed to alleviate distress.

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Review

Significance of angiogenesis in cancer therapy

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Background For most solid tumours, surgery remains the most effective primary treatment. Despite apparently curative resection, significant numbers of patients develop secondary disease due to growth of undetected micrometastases. The ability of a tumour to metastasize is related to the degree of angiogenesis it induces. In addition, micrometastases rely on new vessel formation to provide the nutrients necessary for growth. A better understanding of how tumours acquire their blood supply may lead to more effective adjuvant therapies and improve survival following surgery.

Methods A systematic review of the literature on angiogenesis between 1971 and 1997 was performed using the Medline database to ascertain current thinking on angiogenesis and its relevance in oncological surgery.

Results Angiogenesis is a physiological process subject to autocrine and paracrine regulation which has the potential to become abnormal and play a part in a number of pathological states, including cancer. Increased angiogenic stimuli in the perioperative period, associated with concomitant reduction in tumour-derived antiangiogenic factors following resection of a primary tumour, result in a permissive environment which allows micrometastases to grow.

Conclusion Recognition of the role of angiogenesis in metastatic tumour growth represents a significant development in our understanding of tumour biology. The development of antiangiogenic agents offers new promise in the treatment of malignancy. Such agents may prevent or control the development and growth of primary and metastatic tumours.

Angiogenesis is a process through which new blood vessels develop from pre-existing vessels such as capillaries and postcapillary venules[1,2]. It is tightly regulated by a large number of proangiogenic and antiangiogenic factors. In physiological circumstances, angiogenesis is fully controlled by an equilibrium between these factors such that little blood vessel growth occurs in the healthy adult. Accelerated angiogenesis is a normal physiological response to wound healing, inflammation, menstruation and embryonic development, but a pathological feature of conditions such as diabetic retinopathy, rheumatoid arthritis and solid tumours.

The pivotal role of angiogenesis in primary tumour growth and metastasis has been recognized for many years, although the mechanisms which control it are incompletely understood[3]. Growth of a tumour beyond 2–3 mm^3 requires development of a microvessel network to facilitate delivery of nutrients and oxygen, and removal of catabolites. Density of microvasculature has been used as an indicator of biological aggressiveness and metastatic potential in many primary tumours[4], as neovascularization facilitates metastasis[1,5] by providing access to the circulation[6,7]. The degree of angiogenesis in primary breast[8], prostate[4] and colorectal[9] carcinoma correlates with lymph node metastasis. The predictive value of microvessel density in the primary tumour remains controversial. Microvessel density has been shown to be an independent prognostic indicator in non-small cell lung cancer[10], certain instances of node-negative breast cancer[11,12] and several other carcinomas[13]. However, conflicting reports exist, particularly in relation to its prognostic value in breast cancer[14,15]. These conflicting findings may be attributable, in part, to the heterogeneity of microvessel density within individual tumours, as well as to interlaboratory and interobserver variability in microvessel counting[12].

Our understanding of mechanisms regulating angiogenesis in metastatic disease is increasing[16]. Acquisition of a blood supply by micrometastases at the site of implantation is crucial to tumour growth. Neovascularization is promoted by a number of proangiogenic factors of tumour and stromal origin. The clinical impression that resection of a primary tumour heralds a phase of increased metastatic growth is of particular interest, but until recently no explanation of this phenomenon existed. Recent studies have shown that the intact primary tumour can regulate growth of associated metastases, either directly or indirectly, through the production of certain antiangiogenic factors, notably angiostatin[17]. Surgical excision of a primary tumour removes the source of the inhibitory angiostatin and other factors, allowing angiogenesis and subsequent growth of previously dormant micrometastases[18]. Tumour recurrence many years after apparently successful treatment of a primary lesion is partly the result of increased angiogenesis[19,20]. Long-term suppression of angiogenesis may become a therapeutic option for induction of long-term remission by maintaining micrometastases in a state of dormancy, a dynamic equilibrium during which there is no net tumour growth[20]. The proliferating capillary endothelial cell offers a unique target for antiangiogenic therapy[21] as antiangiogenic strategies may reduce both the recurrence rate and the metastatic potential of solid tumours[22].

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Stages of neovascularization

Newly formed capillaries are composed of two cell types, endothelial cells and pericytes. These two cells have the capacity to produce entire capillary networks. Following the transduction of signals which promote differentiation *in vivo*, angiogenesis progresses in four stages: activation of endothelial cells, proliferation, migration and lumen formation[23].

Cytokine release is provoked by factors endogenous and exogenous to tumour cells, including local environmental factors such as hypoxia. Quiescent endothelial cells are activated by the release of cytokines from host and tumour cells (stage 1). Committed cells proliferate (stage 2), then migrate along a fibrin skeleton towards the source of the angiogenic stimulus to form cords of aligned cells (stage 3). Finally, the vascular sprout forms a lumen and the cells exit the cell cycle to a resting phase. Development of a patent lumen (stage 4) occurs through coalescence of intracellular vacuoles and is facilitated by cell-to-cell adhesive contact[1].

Degradation of the extracellular matrix is an essential component of new vessel invasion. This is facilitated by alteration of the proteolytic balance. Proteolytic degradation of the extracellular matrix and fibrinolysis are two functions of pericytes[24], although pericytes are also thought to contribute by production of growth factors and growth inhibitors. Cell adhesion receptors promote vascular cell migration through interaction with adhesion proteins of the extracellular matrix, such as collagen and fibronectin. The extracellular matrix also serves as a reservoir for growth factors, particularly acidic fibroblast growth factor and basic fibroblast growth factor (bFGF)[25–27].

The capillary sprouts in tumours are 'leaky' as proliferating capillaries have incomplete basement membranes. In addition, vascular endothelial growth factor (VEGF; previously known as vascular permeability factor) increases permeability through the development of a series of interconnected cytoplasmic vesicles and vacuoles (known as vesical-vacuolar organelles) that maintain contact with both the luminal and abluminal surface[28,29]. In normal tissues this may play a regulatory role in controlling baseline microvascular permeability[30], and in tumour microvasculature this feature has been linked to malignant exudates and ascites[31,32].

Regulation of angiogenesis

The degree of angiogenesis in a tumour is the result of complex interactions between tumour cells, capillary endothelial cells, pericytes and recruited immune cells with products of these cells acting in both an autocrine and paracrine fashion[33]. It is normally subject to tight physiological control through a balance of proangiogenic and antiangiogenic factors. These factors allow a phase of rapid proliferation to facilitate wound healing but maintain quiescence in the mature microvasculature[5]. Increased production of positive angiogenic factors is 'necessary but not sufficient'[34] for induction of the angiogenic phenotype; negative regulators must also be decreased[18,35,36]. Imbalance between angiogenic promoters and inhibitors produces the intense angiogenesis which is characteristic of many pathological processes, including diabetic retinopathy[37–39], rheumatoid arthritis[40], endometriosis[41] and malignant tumours[29,42].

Factors influencing angiogenesis are derived both from tumour cells and infiltrating cells, such as macrophages and fibroblasts[7]. Through their secretory products, activated macrophages can influence each phase of the angiogenic process[43–45]. The process of macrophage activation is mediated in part by hypoxia[46]. The large number of macrophages present in a variety of angiogenesis-associated pathological states is indicative of their influence. It is known, for example, that numerous macrophages are present in the first phase of tumour growth. Macrophage density is directly proportional to rate of tumour growth in breast carcinoma[47]. Furthermore, tumour-associated macrophages cause marked augmentation of tumour neovascularization[40] and correlate directly with prognosis in this disease[48]. Other immune cells are also significant, as neutrophilia is associated with a poorer prognosis in breast cancer[49].

Proangiogenic factors (*Table 1*)

Vascular endothelial growth factor

VEGF is the most potent directly acting angiogenic protein known[50]. It is a diffusible endothelial cell-specific

Table 1 Proangiogenic substances

Substance	Reference	Year
Vascular endothelial growth factor	Marme[50]	1996
Basic fibroblast growth factor (FGF-2)	Rifkin and Moscatelli[74]	1989
Acidic fibroblast growth factor (FGF-1)	Jouanneau *et al.*[177]	1995
Platelet-derived endothelial cell growth factor	Takahashi *et al.*[7]	1996
Platelet activating factor	Camussi *et al.*[178]	1995
Transforming growth factor $\beta 1$	Pepper *et al.*[102]	1993
Transforming growth factor α	Gleave *et al.*[179]	1993
Insulin-like growth factor	Nicosia *et al.*[180]	1994
Epidermal growth factor	Goldman *et al.*[181]	1993
Interleukin 1	Fan *et al.*[182]	1993
Interleukin 4	Wojta *et al.*[183]	1993
Interleukin 6	Sunderkotter *et al.*[43]	1994
Interleukin 8	Smith *et al.*[184]	1994
Interleukin 15	Angiolillo *et al.*[185]	1997
Angiogenin	Moenner *et al.*[186]	1994
Vascular integrins $\alpha v_1 \beta_3$ and $\alpha v_1 \beta_5$	Varner and Cheresh[1]	1996
Fibronectin	Bitterman *et al.*[26]	1983
Fibrin	Tsopanoglau *et al.*[187]	1993
Tumour necrosis factor α (*in vivo*)	Frater-Schroder *et al.*[111]	1987
Endotoxin (lipopolysaccharide)	Mattsby-Baltzer *et al.*[112]	1994
Matrix metalloproteinases	Cornelius *et al.*[188]	1995
Scatter factor (hepatocyte growth factor)	Rosen *et al.*[189]	1993
Hyaluron fragments	Cockerill *et al.*[23]	1995
Granulocyte–macrophage colony stimulating factor	Bikfalvi and Han[190]	1994
Platelet activating factor	Bussolino *et al.*[191]	1995
Proliferin	Jackson *et al.*[192]	1994
Substance P	Fan *et al.*[182]	1993
Lactate	Magee *et al.*[193]	1994
Prostaglandin E_1, E_2	Ben-Av *et al.*[194]	1995
Urokinase plasminogen activator	Hildenbrand *et al.*[195]	1995
Tenascin	Canfield and Schor[196]	1995
Nitric oxide	Ziche *et al.*[197]	1994
Erucamide	Mitchell *et al.*[198]	1996

mitogen and angiogenic factor, which also increases vascular permeability[51,52]. It binds to two endothelial cell tyrosine kinase receptors, the fms-like tyrosine kinase (flt) and the kinase domain receptor (KDR)[53,54].

Tumour-derived VEGF plays an important role in the paracrine stimulation of angiogenesis but it also appears to have an autocrine stimulatory effect on tumour cells[55], particularly in response to hypoxia[56]. Hypoxia stimulates angiogenesis in a number of sites, including endothelial cells, retinal pericytes[57], myocardium[58] and solid tumours[59]. VEGF activity is potentiated by oxygen deprivation[60–62], mediated in part by adenosine[57,63] through upregulation of the VEGF endothelial cell receptor KDR[64]. Wild-type *p53*, a tumour suppressor gene, inhibits proliferation of both normal and transformed cells[65,66], and also regulates VEGF production. Mutations in this gene abolish such control. There appear to be two regulatory VEGF pathways: an oncogenic one (v-*src*) that enhances VEGF production and a tumour suppressor (*p53*) signal that suppresses VEGF[50]. Mutations of the *ras* oncogene cause VEGF upregulation in a colon cancer model with resulting increased angiogenesis[67]. H-*ras* oncogene mutation also activates angiogenesis through upregulation of VEGF and matrix metalloproteinase (MMP) bioactivity, while downregulating activity of tissue inhibitors of MMP[68].

Tumour cell lines which express minimal constitutive and hypoxia-inducible VEGF (e.g. human melanoma SK-MEL-2 cells) produce small, poorly vascularized tumours. Overexpression of VEGF results in dramatically increased angiogenesis and subsequent tumour expansion[69]. Interruption of the VEGF receptor paracrine pathway in glioma tumours inhibits angiogenesis, leading to reduced numbers of new vessels, a higher degree of necrosis and a reduction in size of glioma tumours[70]. Expression of VEGF and its receptor KDR is higher in metastatic than in non-metastatic colonic neoplasms, and correlates directly with the extent of neovascularization and degree of proliferation[9]. There is a direct correlation between serum VEGF concentration and breast cancer stage[71].

Soluble recombinant flt receptor binds to free VEGF and inhibits its mitogenic affinity for endothelial cells[72]. Anti-VEGF antibodies have been used as a new therapeutic modality for the prevention of retinal ischaemia-induced neovascularization of the iris, confirming that the *in vitro* effects of VEGF inhibition are reproducible *in vivo*[73].

Basic fibroblast growth factor

This is a 16-kDa protein which is one of a family of fibroblast growth factors[74]. Capillary endothelial cells themselves produce and release bFGF which acts in an autocrine fashion independently, and synergistically with VEGF[75], as an endothelial cell mitogen[76]. It binds intensely to the extracellular matrix, but is normally confined to its cell of origin as it lacks the signal peptide thought to be necessary for secretion[50]. During the malignant evolution of fibrosarcoma, neovascularization is associated with a switch to the ability to export bFGF from cells[77]. It also stimulates endothelial and vascular smooth muscle cell motility[78,79] especially after arterial trauma[80]. Heparin released by recruited mast cells amplifies its effect[5]. Its systemic administration results in an increased rate of tumour growth and increased vascularity[81]. Binding by bFGF is inhibited by suramin, an antiparasitic agent[82]. It has been shown that blockade of bFGF receptors results in suppression of solid tumour growth[83].

Acidic fibroblast growth factor

This is a heparin binding site-specific endothelial cell mitogen[84,85] which promotes angiogenesis and wound healing[86,87]. It is expressed constitutively in normal as well as in tumour cells, but appears to be inhibited by an angiogenesis suppressor gene which is downregulated during tumorigenesis[34]. Like bFGF, it is found in many normal cells but exported only in tumour cells.

Platelet-derived endothelial cell growth factor

This proangiogenic cytokine is found in platelets[88] and released during the blood clotting cascade, as well as being produced by vascular smooth muscle cells[89]. It is an endothelial cell mitogen but is not a classical growth factor, because direct contact with a cell-surface receptor is not required for its mitogenic capability[90]. It promotes endothelial cell migration[91] and may facilitate endothelial differentiation[92]. Platelet-derived endothelial cell growth factor (PD-ECGF) expression is known to be modulated by the tumour microenvironment[93]. It is homologous to thymidine phosphorylase[94], an enzyme which catalyses the reversible breakdown of thymidine to thymine and deoxyribose-1-phosphate. This enzymatic activity may contribute to its angiogenic activity, as products of deoxyribose-1-phosphate are known to be angiogenic, although the mechanism through which PD-ECGF exerts is angiogenic effect is not yet fully understood[95,96].

Transforming growth factor β

Transforming growth factor (TGF) β, which is produced by macrophages and activated platelets, exists in three human isoforms, $\beta 1$, $\beta 2$ and $\beta 3$. All act as chemotactic agents for macrophages and are indirectly angiogenic *in vivo*[97–100], although TGF $\beta 1$ appears most potent in this regard[100]. TGF $\beta 1$ facilitates wound healing through accelerated collagen deposition and maturation[101]. It induces matrix production and alters integrin production to facilitate neovascularization. It acts in a dose-dependent manner, with low concentrations exhibiting stimulatory and high concentrations inhibitory effects[102]. Its absence results in poor vascular integrity and reduced remodelling[103]. TGF $\beta 3$ appears to have a greater role in matrix remodelling, with a resultant decrease in scar formation[100].

Epithelial growth factor

Epidermal growth factor (EGF) is a mitogenic growth factor. EGF receptors belong to a group of proto-oncogenes, including c-*erbB2*, which are overexpressed in a number of human tumours[104]. EGF is secreted by tumour-associated macrophages in patients with carcinoma of the breast[105].

Integrins

Blood vessels involved in angiogenesis express adhesion proteins, known as integrins, including von Willebrand factor, fibronectin, fibrin and vascular integrin $\alpha v_1 \beta_3$ and $\alpha v_1 \beta_5$. They facilitate cell–cell and cell–matrix interactions[106], thereby playing a crucial role in endothelial cell chemotaxis. Adhesion proteins may be selectively inhibited by monoclonal antibodies with the resulting decrease in angiogenesis inducing apoptosis of endothelial cells[34]. Vascular integrin $\alpha v_1\beta_3$ is selectively expressed on growing vessels, where it suppresses p53 activity while increasing the *bcl2*:*bax* ratio with a net proangiogenic and antiapoptotic effect[107]. Its inhibition by monoclonal antibodies in a melanoma model results in reduced angiogenesis, suggesting that the new tumour vasculature grows in a self-perpetuating manner[108].

Tumour necrosis factor α

Tumour necrosis factor (TNF) α is a macrophage-derived angiogenic factor which is considered to be the principal mediator of tumour cell cytotoxicity and cytostasis[109]. It has a broad spectrum of biological activities including both stimulatory and inhibitory effects on target cells which are dose related[40,110]. It induces granulocyte–macrophage colony stimulating factor production, has procoagulant activity and increases the adherence of human endothelial cells. Its proangiogenic activity was initially postulated to be induced through an inflammatory mechanism secondary to its cytotoxic effects[111]. It is now believed that TNF-α is a potent mediator of angiogenesis at low concentrations, independent of inflammation[110].

Endotoxin

Endotoxin (lipopolysaccharide; LPS) is a ubiquitous molecule derived from the cell wall of most Gram-negative and some Gram-positive bacteria as well as existing in a free form in the environment. It is a proangiogenic molecule because of its ability to elicit production of a wide spectrum of host-effector molecules, such as VEGF, bFGF, TGF-β, TNF, interleukin (IL) 1 and IL-6, by macrophages and other cell populations[112–114]. Recent work from the authors' laboratory shows that LPS introduced at the time of open surgery in a tumour-bearing murine model increases serum VEGF concentration[115].

Antiangiogenic factors (*Table 2*)

Thrombospondin

Thrombospondin is a glycoprotein secreted by many cells, including endothelial and epithelial cells, fibroblasts, smooth muscle cells, monocytes and macrophages[116]. It modulates endothelial cell adhesiveness, motility and proteolytic activity by sequestering angiogenesis inducers[117]. While it is a potent inhibitor of angiogenesis, it is downregulated during tumorigenesis[5,118,119]. In fibroblasts, wild-type p53 inhibits angiogenesis through upregulation of thrombospondin[33], an effect which is abolished by p53 mutations. Paradoxically, thrombospondin enhances the angiogenic effect of LPS and bFGF stimuli in inflammatory states[120]. It is speculated that thrombospondin 1 downregulates VEGF expression through an as yet unknown mechanism[48].

Angiostatin

Angiostatin is a 38-kDa internal fragment of plasminogen[121] which inhibits endothelial cell proliferation, angiogenesis and tumour growth. It blocks the catalytic site of the enzyme that cleaves plasminogen, thereby preventing the matrix remodelling required for angiogenesis[117]. It selectively prevents endothelial cells responding to angiogenic stimuli resulting in dormancy of micrometastases[122]. Systemic administration has been shown to induce regression of primary tumours of breast, colon and prostate in a murine model, providing the first example of dormancy therapy in which tumours undergo regression through blockade of angiogenesis[17].

Table 2 Antiangiogenic substances

Substance	Reference	Year
Thrombospondin	Canfield and Schor[196]	1995
Angiostatin	O'Reilly *et al.*[121]	1994
Endostatin	O'Reilly *et al.*[123]	1997
Suramin	Takano *et al.*[170]	1994
Interferon α and β	Stout *et al.*[168]	1993
Interferon γ	Kobayashi *et al.*[199]	1995
Interferon μ inducible protein 10	Angiolillo *et al.*[200]	1996
Interleukin 12	Voest *et al.*[169]	1995
Tamoxifen	Donovan *et al.*[32]	1997
Thalidomide	D'Amato *et al.*[158]	1994
Linomide	Vukanovic and Isaacs[201]	1995
Fumagillin analogues (AGM-1470)	Klauber *et al.*[160]	1997
Captopril	Volpert *et al.*[202]	1996
Platelet factor 4	Strieter *et al.*[203]	1995
Antisense VEGF RNA, VEGF blocking antibody and VEGF receptor kinase inhibitors	Millauer *et al.*[204]	1996
Transforming growth factor β1	Pepper *et al.*[102]	1993
Proliferin-related protein	Jackson *et al.*[192]	1994
2-methoxyoestradiol	Fotsis *et al.*[205]	1994
Tissue inhibitor of metalloproteinase	Tagikawa *et al.*[206]	1990
Retinoids	Pienta *et al.*[207]	1993
Tumour necrosis factor α (*in vitro*)	Frater-Schroder *et al.*[111]	1987
Group B *Streptococcus* toxin CM 101	Thurman *et al.*[208]	1996
Pentosan polysulphate	Nguyen *et al.*[209]	1993
Lavendustin A	Hu and Fan[210]	1995
Dexamethasone	Hori *et al.*[211]	1996
Medroxyprogesterone acetate	Yamamoto *et al.*[212]	1994
Korean misletoe extract (*Viscum album coloratum*)	Yoon *et al.*[213]	1995
Indomethacin	Tarnawski *et al.*[214]	1989
Diclofenac	Lala *et al.*[215]	1997

VEGF, vascular endothelial growth factor

Endostatin

Endostatin is a protein fragment of collagen XVIII and was first isolated from a murine haemangioendothelioma cell line[123]. It acts in a similar way to angiostatin, blocking collagenase and impeding matrix remodelling. It specifically inhibits endothelial cell proliferation. Recombinant endostatin inhibits angiogenesis, growth of metastases and growth of primary tumours[123]. Endostatin-treated tumours have a proliferation rate which is the same as that of untreated tumours, but an apoptotic rate which is sevenfold greater, providing a further example of dormancy therapy.

Tumour angiogenesis

Malignant transformation is a cumulative process requiring loss of control of the cell cycle and a shift in the balance of proangiogenic and antiangiogenic factors. Induction of angiogenesis is a local event which is specific to activated hyperplastic cells and which procedes overt tumour formation[124]. For example, angiogenesis is a marker of premalignant transformation in benign breast disease[125,126]. Vascular endothelial cells in malignant breast tumours express tissue factor, a potent procoagulant, whereas vascular endothelial cells in benign tumours do not[127]. Cell proliferation and malignant transformation represent a switch to an angiogenic phenotype, but only in the latter is control of the cell cycle lost. Furthermore, only those hyperplastic cells which acquire angiogenic capacity undergo malignant transformation[124,126]. One model involves a tumour suppressor gene encoding the angiogenesis inhibitory factor thrombospondin, which is downregulated when cells undergo malignant transformation, allowing the angiogenic phase to commence[118]. This downregulation is under the control of the *p53* tumour suppressor gene[33]. Loss of suppressor gene sequences[128] leads to failure of inhibitory pathways with resultant tumour growth[110].

Numerous parallels between wound healing and tumour growth exist, suggesting that tumours act as 'obligate parasites' which have developed the capacity to pre-empt and subvert the wound healing response of the host as a means to acquire the stroma they need to grow and expand[129]. Normal cells involved in wound healing, such as endothelial cells and fibroblasts, develop features similar to those of malignant cells[130]. These features include increased proteolysis[131], increased motility[132] and proliferation. It is postulated that the invasive, proliferative behaviour of transformed cells may result from a functional failure of signals that usually regulate the activated behaviour of normal cells in a wound[129].

Angiogenesis and tumour metastasis

Tumour cells must detach from a primary tumour to initiate the 'metastatic cascade'[19,133]. Angiogenesis is a necessary precursor of metastasis as new proliferating capillaries have incomplete basement membranes and are 'leaky', facilitating penetrance by tumour cells[134,135]. These tumour cells must evade immune surveillance in the circulation and also at the site of secondary development, where they cross endothelium, degrade basement membrane, implant, proliferate and establish their own capillary network[19]. Angiogenesis is necessary at both the beginning and the end of the metastatic cascade. There is resultant metastatic inefficiency as only a small number of tumour cells which leave the primary tumour successfully implant at distant sites[136,137].

Effect of surgery on angiogenesis

Clinical experience and experimental evidence support the concept that the healing wound is an immunologically privileged site for metastases[25,106,138,139]. The cytokine environment that ensues in the first 24 h following surgical trauma influences the healing process for the subsequent 3 weeks[101]. Tumour growth is enhanced in healing wounds, but not in surrounding normal tissues. It has been shown that when tumour cells reach a healing colonic anastomosis or laparotomy wound within 2 h of its formation, the probability of a tumour cell leading to a metastatic deposit is increased 1000-fold compared with normal tissue[140]. Evidence showing an increased hazard rate for relapse or death in the 3 years following surgery for breast cancer, and a second peak a number of years later, supports the theory that micrometastases with a variable rate of growth are present at the time of diagnosis[141]. Surgery and subsequent healing may contribute to the genesis of recurrent disease through promotion of a proangiogenic climate which alters the dynamic equilibrium that would otherwise maintain micrometastases in a state of dormancy[20,142] (*Fig. 1*).

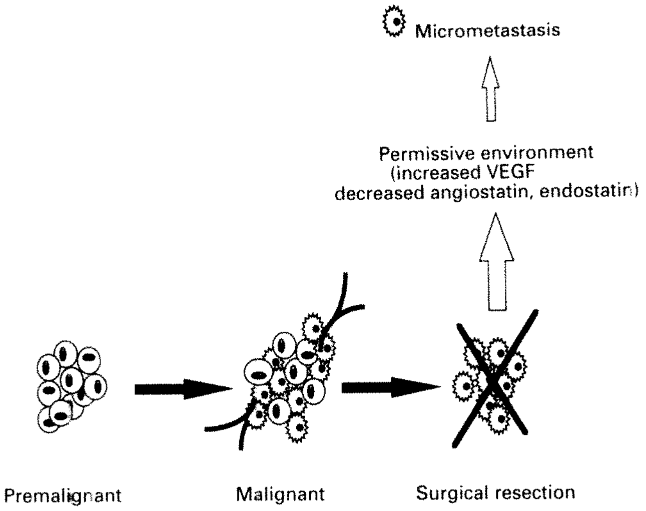

Fig. 1 Effect of surgery on micrometastases. VEGF, vascular endothelial growth factor; LPS, lipopolysaccharide

VEGF may be one of the primary links between these observations, as it is necessary to allow wound healing but may also foster growth of micrometastases through its potent proangiogenic activity. Raised circulating levels of VEGF have been identified in the early postoperative period (J. H. Harmey, unpublished observation). This may facilitate the growth and metastasis of circulating or intravasated dormant tumour cells.

Endotoxin induces angiogenesis in a dose-dependent fashion at biologically relevant doses[112]. Significant translocation of endotoxin into the peritoneal cavity and systemic circulation occurs following open surgery or air-insufflation laparoscopy[143]. It directly increases macrophage production of VEGF, a potent angiogenic factor regulating both vessel growth and permeability, an effect which also appears to extend to tumour cells[115,144]. Surgical trauma is known to increase leucocyte numbers and activity[145] and to promote tumour establishment and growth[146]. The authors' preliminary observations indicate that endotoxin introduced at the time of surgery may encourage the growth of metastases by suppression of host antitumour immune function and stimulation of proangiogenic factor release. The result is a permissive environment for tumour growth and angiogenesis.

It has been shown that the primary tumour produces circulating inhibitors of angiogenesis, called angiostatin and endostatin, which act specifically at the level of endothelial cell proliferation[121]. Within 5 days of removal of the primary tumour, angiostatin and endostatin disappear from the circulation and angiogenesis within dormant micrometastases becomes possible. This heralds a phase of rapid growth of previously dormant micrometastases[18]. Dormancy is normally maintained in tumour cells by means of a high replication rate and a correspondingly high apoptotic rate (*Fig. 2*). There is no change in the replication rate of neovascularized

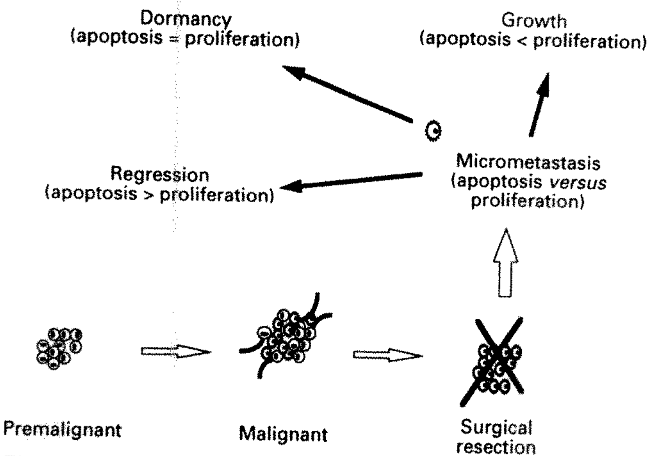
Dormancy
(apoptosis = proliferation)
Growth
(apoptosis < proliferation)
Regression
(apoptosis > proliferation)
Micrometastasis
(apoptosis *versus* proliferation)
Premalignant
Malignant
Surgical resection

Fig. 2 Fate of micrometastases

metastases; however, the apoptotic rate is significantly decreased with resultant net metastatic growth[20].

Therapeutic opportunities (*Fig. 3*)

The aim of antiangiogenic treatment is to reduce and maintain tumours as small relatively dormant clusters of cells which have low metastatic potential, are more susceptible to cell-mediated immunological attack[3], and which may be more vulnerable to chemotherapy[147] and radiotherapy[148,149]. Tumour growth is associated with increased interstitial pressure due to leaky tumour vessels[150] in the absence of adequate lymphatic vessels[151]. This causes vascular compression and eventual central necrosis. As a result, tumours do not outgrow their blood supply, they compress it[152]. Antiangiogenic therapy paradoxically increases delivery of chemotherapy to a tumour[147] by reducing interstitial pressure[152]. Inhibition of angiogenesis results predominantly in a cytostatic, not a cytotoxic, effect[22,153–155], although a recent study suggests that antiangiogenic therapy may lead to tumour regression[156].

Successful antiangiogenic strategies have incorporated a wide range of antiangiogenic agents[121,157–163]. Prolonged courses of interferon α induce regression of human haemangiomatous disease[164]. Systemic administration of angiostatin induces regression of primary murine tumours of breast, colon and prostate[17]. Recombinant endostatin inhibits angiogenesis, the growth of metastases and the growth of primary tumours[123]. *In vivo* inhibition of angiogenesis using an animal model of pancreatic carcinoma has been shown to reduce tumour growth[165].

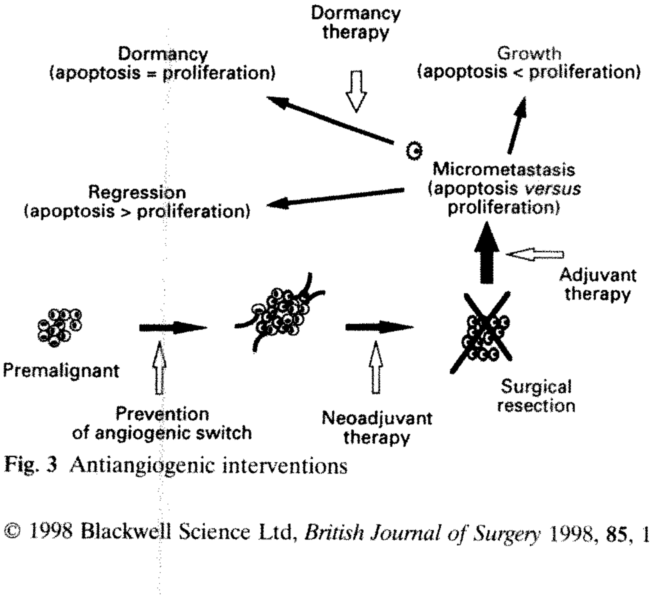
Dormancy therapy
Dormancy
(apoptosis = proliferation)
Growth
(apoptosis < proliferation)
Regression
(apoptosis > proliferation)
Micrometastasis
(apoptosis *versus* proliferation)
Adjuvant therapy
Premalignant
Prevention of angiogenic switch
Neoadjuvant therapy
Surgical resection

Fig. 3 Antiangiogenic interventions

Mechanisms of action

Antiangiogenic therapies may act either directly, by specifically inhibiting endothelial cell proliferation, or indirectly, by altering the cytokine microenvironment which controls angiogenesis. Tumours consist of a 'two-compartment system' in which tumour cells and endothelial cells co-exist, and produce growth factors which have paracrine effects on each other[33]. Inhibition of endothelial cell growth reduces production of tumour-promoting substances and inhibits tumour expansion. Inadequate tumour vascularization may result in tumour cell apoptosis, a genetically programmed form of cell death[36]. Dormant micrometastases are biologically active with a rate of apoptosis equal to their rate of cell proliferation[122,166]. As a result, no net growth of the metastasis occurs. Antiangiogenic therapies promote and maintain perpetual dormancy by increasing the apoptotic rate within the metastasis, hence the appellation 'dormancy therapy'.

Direct antiangiogenic agents

Angiostatin and endostatin are the only direct inhibitors of angiogenesis identified to date, and both have been shown to reduce tumour growth[121,123]. Systemic administration of endostatin, which directly inhibits endothelial cell mitogenesis, has been suggested as an ideal 'dormancy therapy'[123]. More recently, it has been reported that repeated cycles of endostatin can prevent tumour recurrence, possibly through the induction of an antiangiogenic phenotype, without leading to the problems of drug resistance which characterize many chemotherapeutic agents[156]. Hanahan[167] has suggested that direct inhibitors of angiogenesis may be subdivided into three groups. First, pure angiogenesis inhibitors, which inhibit new vessel growth but have no effect on existing tumour vessels. Second, tumour vessel toxins, which damage existing tumour vasculature and, finally, dual action agents, which combine these two effects. It appears that endostatin is a member of the last group.

Indirect antiangiogenic agents

Indirectly acting antiangiogenic therapies influence the microenvironment which regulates tumour angiogenesis and so indirectly influence endothelial cell behaviour. The majority of antiangiogenic agents currently identified belong to this group. Each tumour has a unique complex microenvironment dictated both by tumour histology and site of implantation. Additionally, within any tumour, heterogeneity arises because of variations in stromal density, tumour differentiation, hypoxia and local cytokines, among other factors. As a result, each tumour is exposed to different proangiogenic and antiangiogenic stimuli which ultimately influence net angiogenesis. It is therefore unlikely that therapeutic manipulation of a single cytokine will be sufficient to regulate tumour angiogenesis adequately. Intertumour variability suggests that therapeutic regimens based on cytokine manipulation must be custom-designed for each particular tumour type.

Maximum clinical gain may potentially be achieved by a combination of antiangiogenic interventions which influence different aspects of angiogenesis. For example, the fumagillin analogue AGM-1470 reduces endothelial cell proliferation[157]. Interferon α interferes with endothelial cell migration[168] and IL-12 inhibits angiogenesis mediated by interferon γ[169]. In contrast, suramin inhibits bFGF receptor binding in addition to a number of direct effects on endothelial cells[170], while tamoxifen inhibits VEGF-mediated endothelial cell proliferation and migration[171]. Direct manipulation of endothelial cell proliferation combined with alteration of the cytokine microenvironment may prove more effective than either approach alone.

Multimodality therapy, in which antiangiogenic strategies are combined with chemotherapeutic agents or radiotherapy, is known to be more effective than monotherapy, probably because of the combined effects on both the tumour and vascular compartments[147–149,172].

Optimal methods and timing of administration of antiangiogenic therapies have yet to be determined. Unfocused interruption of angiogenesis may potentially interfere with wound healing, menstruation and embryogenesis. Inhibitors of endothelial-specific growth factors (e.g. VEGF) have a theoretical advantage over inhibition of growth factors with more widespread targets (e.g. bFGF) because undesired non-specific interruption of mitogenesis is avoided. However, it is likely that novel methods of site-specific drug delivery, developed to administer experimental proangiogenic therapies in the treatment of ischaemic heart disease, will also be applied to the delivery of antiangiogenic agents and may help to reduce unwanted systemic effects[56]. Substantial expression of VEGF receptors is predominantly limited to the tumour vasculature. Interference with this system using monoclonal antibodies, dominant negative receptor or antisense oligonucleotides against VEGF messenger RNA offer the potential of tumour-specific inhibition of angiogenesis and subsequent metastatic growth[173]. A similar approach could be pursued for other cytokines. Developments in the field of gene therapy[174] may be harnessed to produce long-term low-grade antiangiogenic substances which maintain micrometastases in a state of dormancy.

The dosing schedule for biological antiangiogenic agents is likely to differ significantly from that for pharmaceutical agents[18]. Clinical experience with interferon α in the treatment of life-threatening haemangiomas has shown that very prolonged courses of daily therapy at optimal doses are essential for vessel involution[175]. Timing of antiangiogenic therapy in relation to other therapeutic interventions also requires clarification. For example, excision of a primary tumour results in decreased levels of the inhibitory factors angiostatin and endostatin[18], and raised circulating levels of VEGF. In the postoperative setting, this is likely to facilitate the growth and metastasis of circulating or dormant tumour cells. Therefore, manipulation of tumour angiogenesis in the perioperative period provides a tempting therapeutic opportunity. The effect of impaired angiogenesis on wound healing, however, must be clarified. A balance between the neovascularization necessary for wound healing and inhibition of neoplastic microvessel formation must be achieved.

Variability in mechanisms and control of angiogenesis at different stages in the natural history of cancer may exist. A premalignant phase is recognized for many tumours. This is also a preangiogenic phase and development of an antiangiogenic strategy which prevents the onset of angiogenesis could prevent progression to a malignant state[176]. This would require both identification of premalignant cells and development of an appropriate prophylactic antiangiogenic regimen. This is likely to differ substantially from the therapeutic approach required for primary tumours or micrometastases. For example, VEGF messenger RNA expression develops late in the course of tumour progression, is not a feature of premalignancy[28] and its manipulation is, therefore, unlikely to be of benefit in this situation. Timing of prophylactic therapy will also be critical, as angiogenesis is probably not involved in the interim stage of micrometastasis following shedding from the primary tumour, when micrometastases are distributed in organs as either single cells or small clusters with ready access to a blood supply[20]. None the less, inhibition of angiogenesis is the most promising new therapy in the treatment of malignancy. Complete understanding of the factors regulating angiogenesis and the interactions between these factors should lead to valuable new interventions. These may be combined with surgery and other modalities to improve the treatment of many solid tumours.

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SURGERY TODAY
The Japanese Journal of Surgery

Digest

Professor Keizo Sugimachi, Editor-in-Chief of *Surgery Today* (*The Japanese Journal of Surgery*), has selected from the October to December 1997 issues of his journal for this quarter's digest. A digest of *BJS* for the same period written by Mr Colin Johnson, European Editor, appears in the Japanese journal.

Stomach cancer

While proximal gastrectomy is often performed for early gastric cancer in Japan, it remains unclear whether or not the procedure should be performed for advanced gastric cancer. A study[1] was designed to determine the operative indications for proximal gastrectomy in patients with gastric cancer in the upper third of the stomach. A total of 1691 patients with gastric cancer were reviewed retrospectively from hospital records covering the period from 1969 to 1994, and the clinicopathological characteristics of 82 patients who underwent proximal gastrectomy were compared with those of 150 patients who underwent total gastrectomy. Lymph node metastasis along the lower part of the stomach was observed in gastric cancers which had invaded beyond the muscularis propria of the stomach, but not in those confined to the muscularis propria. Three patients with gastric cancer that had invaded beyond the muscularis propria and metastasized to nodes along the lower part of the stomach were cured by total gastrectomy. However, there was no difference in the postoperative survival rates of patients treated with proximal gastrectomy and those treated with total gastrectomy, irrespective of tumour stage and depth of invasion. Thus, proximal gastrectomy should be performed for gastric cancer when invasion is confined to the muscularis propria of the stomach.

Rectal carcinoma

Preservation of the pelvic plexus in surgery for rectal cancer could shorten the distance between the cancer and the lateral resection margin, which may reduce the effectiveness of the operation. To clarify the indications for preserving the pelvic plexus in such surgery, the relationship of the pelvic plexus to the rectum and rectal cancer was investigated anatomically in 12 autopsy specimens and 12 surgical specimens[2]. The rectum and anus were dissected with all the pelvic organs from cadavers and transverse sections were prepared at 10-mm intervals after fixation. The location of the pelvic plexus was measured on the tissue samples and compared with that of surgical specimens from rectal cancers with concurrent resection of the pelvic plexus. The pelvic plexus was located from a mean(s.d.) of 3·3(1·2) cm above to 2·3(1·9) cm below the peritoneal reflection in the autopsy specimens. The mean distances between the muscularis propria and the pelvic plexus in the autopsy specimens and surgical specimens were 8·3(3·5) and 14·7(4·5) mm respectively ($P < 0·05$). Pelvic plexuses were located about 10 mm from the outer margin of the rectal muscularis propria. These findings indicate that concurrent resection of the plexus may be required to secure sufficient surgical clearance in pT_3 rectal cancers, especially those invading deeply beyond the muscularis propria (a_2).

The complications that may develop after preoperative intraluminal brachytherapy (IBT) and radical surgery for rectal carcinoma have been reviewed[3]. A total of 106 patients with rectal carcinoma who were given moderate (16–40 Gy) or high (40–80 Gy) doses of IBT between 1986 and 1995 were followed in the outpatient clinic. Postoperative complications developed in 34 of 87 patients in the moderate-dose group and 13 of 19 patients in the high-dose group; seven of those in the former group and five in the latter group required surgical intervention for the complication. The other patients were treated conservatively. Statistical analysis identified factors related to the incidence of complications to be the IBT dose, the field length, the time–dose factor, and the distance from above the anal verge to the distal border of the tumour. The incidence and severity of complications suggested that moderate-dose IBT was better than high-dose IBT before operation, especially when restorative operations were scheduled.

A retrospective study was conducted to identify factors related to locoregional recurrence in patients who underwent curative resection for primary rectal cancer between January 1986 and April 1994 at Ankara Oncology Hospital in Turkey[4]. A stepwise logistic regression analysis was applied for 116 patients who had complete follow-up. Age, sex, macroscopic size of the lesion, tumour location in the rectum as determined by the distance from the anal verge, obstruction at presentation, tumour histology, lymphatic invasion, venous invasion, stage according to the tumour node metastasis classification, differentiation of the tumour, surgical treatment modality, radical abdominopelvic lymphadenectomy (RAPL) and blood transfusion were used as the clinicopathological variables. Locoregional recurrent disease was found after a mean follow-up of 52 months in 28 patients (24 per cent), while the median recurrence-free period was 12 months. Univariate analysis demonstrated that age, disease stage, tumour grade, obstruction, RAPL, blood transfusion, and venous and lymphatic invasion were significant risk factors ($P < 0·05$); however, using multivariate analysis, an increased risk for the development of locoregional recurrence was found to be associated with age ($P = 0·0052$), stage ($P = 0·0379$), blood transfusion ($P = 0·0276$), obstruction ($P = 0·0035$) and RAPL ($P = 0·0069$).

Lung tumour

Between 1969 and 1995, 180 patients underwent complete resection of lung metastases during initial thoracotomy, involving the resection of 917 pulmonary nodules at 202 thoracotomy procedures[5]. The overall 5- and 10-year survival rates after metastasectomy were 46 and 30 per cent respectively. Of 111 patients who underwent segmentectomy and/or local excision, 57 had multiple metastases, 39 of whom were treated by neodymium yttrium–aluminium–garnet (NdYAG) laser after 1986 and 18 by conventional procedures before 1985. The mean number of tumours resected per patient treated with the NdYAG laser was significantly greater than that of those treated with conventional procedures. However, the survival curve of the laser-treated group was better than that of those treated conventionally. Moreover, slightly better survival was achieved in patients operated on after 1992 compared with those operated on before 1991. It is concluded that the laser technique may be warranted to afford complete resection of metastases and adequate pulmonary preservation in combination with a selective approach for thoracotomy, with careful tumour localization using the most recent high-quality computed tomography. Furthermore, a one-stage operation to control synchronous intrapulmonary and extrapulmonary malignancies may become a possible option in combination with selective adjunctive therapy.

In patients who are unable to undergo lobectomy for a small peripheral lung cancer, a partial thoracoscopic resection appears to be one valuable alternative[6]. However, since the regional lymphatics are disrupted in an anatomical fashion with a segmentectomy, it appears superior to a wedge resection. This experimental study was conducted to determine whether or not an anatomical segmental resection is feasible by thoracoscopy. A segmental resection of porcine lungs was performed using thoracoscopy. The segmental vessels were divided between ligatures. The segmental bronchus was divided by an endoscopic stapler. The intersegmental lung parenchyma was divided using a cotton dissector and a contact NdYAG laser. Forty-three pigs were divided into seven groups as follows: group 1, S^{1+2}; group 2, S^3; group 3, upper division; group 4, lower division; group 5, S^6; group 6, S^8; and group 7, S^{9+10}. The mean(s.d.) operating times ranged from 145(15) to 191(47) min. Mean(s.d.) blood loss ranged from 36(35) to 151(48) ml in all groups. The blood loss in the groups with a resection of S^6 and S^{9+10} was significantly greater than that of the other five groups. Most of the blood loss occurred during the division between the intersegmental planes. In conclusion, a thoracoscopic segmentectomy is considered to be technically feasible; however, further refinements to this technique are warranted before beginning clinical trials.

Breast tumour

The clinical and pathological features of phyllodes tumours of the breast were evaluated in a study of 118 cases: 110 benign tumours, four borderline tumours and four malignant tumours[7]. Local excision was performed in 105 patients (89 per cent) and radical mastectomy was performed in ten patients (8 per cent) as the initial treatment. Oestrogen receptor status was positive in seven of 14 cases and progesterone receptor status was positive in nine of 12 cases. Local recurrence developed in eight patients, six with benign tumours and two with malignant tumours, all of whom were treated by local excision. Of the four patients with malignant tumours, one died from lung and liver metastases 47 months after the first operation. The authors believe that excision with a sufficient free margin may be the treatment of choice for most benign or borderline phyllodes tumours, whereas an Auchincloss modified radical mastectomy or a total glandectomy with lymph node dissection is recommended for patients with malignant tumours. However, a number of problems regarding the treatment of patients with distant metastasis remain to be addressed.

To investigate the impact of the number of involved lymph nodes on survival, the data for 37 patients with breast cancer and metastases of ten or more lymph nodes, who underwent treatment between 1987 and 1995, were reviewed[8]. Based on the number of positive lymph nodes, the patients were allocated to one of three groups. The 5-year disease-free and overall survival rates for all patients were both 53 per cent. The seven patients with 26 or more positive nodes had significantly poorer survival than either the 19 patients with ten to 15 nodes or the 11 with 16 to 25 nodes, although there were no differences in survival related to the extent of nodal involvement, defined using the Japanese staging system. Patients with a 50–75 per cent frequency of metastasis, defined as the ratio of positive nodes to total resected nodes, had significantly better survival than those with a frequency of less than 50 per cent or more than 75 per cent. These results indicate that the number of involved lymph nodes is related to survival and that 25 positive nodes is a cut-off point in patients with breast cancer with ten or more positive lymph nodes.

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Central venous pressure and its effect on blood loss during liver resection

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Background Any strategy to reduce blood loss in liver resection and decrease blood transfusion would be of benefit to the patient and surgeon. This study evaluates the association of central venous pressure (CVP) with blood loss and blood transfusion during liver resection.

Methods One hundred consecutive hepatic resections in the period 1986–1996 were studied prospectively concerning CVP, volume of blood lost, and volume of blood transfused. Blood loss volume and blood transfusion were analysed for those with a CVP less than or equal to 5 cmH_2O, and greater than 5 cmH_2O. A multivariate analysis assessed potential confounding factors in the comparison.

Results The median blood loss in patients with a CVP of 5 cmH_2O or less was 200 ml ($n = 40$) and that in those with a CVP above 5 cmH_2O was 1000 ml ($n = 52$) ($P = 0·0001$). Only two of 40 patients with a CVP of 5 cmH_2O or less had a blood transfusion whereas 25 of 52 patients with a CVP greater than 5 cmH_2O required a transfusion ($P = 0·0008$). A multivariate analysis did not show confounding factors.

Conclusion The volume of blood lost during liver resection correlates with the CVP. Lowering the CVP to less than 5 cmH_2O is a simple and effective way to reduce blood loss during liver surgery.

Hepatic resection can be associated with significant intraoperative blood loss and the need for transfusion of blood and blood products[1-5], exposing the patient to the risks of transfusion. In addition, significant bleeding prolongs liver dissection and portal occlusion time, increasing the hepatic ischaemia–reperfusion injury. Any strategy that reduces blood loss during liver resection would benefit both the patient and surgeon. In addition to portal occlusion, various other devascularization manoeuvres have been designed to decrease blood loss[6-9]. Total vascular exclusion (TVE) has been used selectively but has been associated with significant risks and complications[6,7]. TVE cannot be used in all patients because of the reduction in cardiac output and consequent hypotension. Venovenous bypass can reduce the frequency of these complications but adds to the time and the complexity of the procedure.

Clamping of the structures in the lesser omentum, which occludes the inflow of blood through the hepatic artery and the portal vein to the liver[10], can be performed safely, quickly and is used widely[6,11-13]. However, the hepatic veins remain patent and bleeding may continue from them and from the sinusoids. The pressure within the sinusoids of the liver parenchyma is directly related to the pressure in the hepatic veins, which is directly related to the pressure in the central veins. The hypothesis was that a low pressure in the central veins would be accompanied by a low pressure in the hepatic veins and sinusoids, thereby decreasing blood loss during transection of the liver parenchyma. The aim of this study was to analyse the relation of central venous pressure (CVP) to blood loss during liver resection, including a multivariate analysis of possible confounding factors.

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Patients and methods

One hundred consecutive hepatic resections, performed between 1986 and 1996, were documented prospectively. There were 48 men and 52 women with a mean(s.e.) age of 51·2(1·4) years. The indications for liver resection are outlined in *Table 1*. The liver resections were: right hemihepatectomy (Couinaud segments V–VIII) (20); left hemihepatectomy (segments II–IV) (14); right lobectomy (segments I, IV–VIII) (16); left lobectomy (segments II–III) (ten); segmentectomy (30); and subsegmentectomy (ten). Ten resections were performed in patients with cirrhosis. Data collected prospectively included age, sex, intercurrent disease, length of operation, operation performed, number of lesions resected, length of portal vein and hepatic artery occlusion, CVP, volume of intraoperative blood loss, and intraoperative and postoperative blood transfusion.

Arterial and central venous access and end-tidal carbon dioxide monitoring were used in all patients. The abdominal incision was either a reversed L or a Mercedes Benz type. A thoracic extension was used on one patient. Intraoperative ultrasonography was used routinely to identify the location and extent of disease and intrahepatic anatomy (Ultrasound SSD 248 with 7·5- and 5-MHz T-piece probes; Aloka, Tokyo, Japan). The portal triad was dissected and then clamped during parenchymal dissection (70 patients). The liver parenchyma was divided using blunt dissection in 46 instances and with the Cavitron Ultrasonic Surgical Aspirator (CUSA; Valleylab, Boulder, Colorado, USA)

Table 1 Indications for liver resection

Indication for resection	No. of patients
Colorectal metastases	52
Other metastases	15
Hepatomas	10
Hydatid disease	12
Focal nodular hyperplasia	8
Haemangiomas	3

in 54. Haemostasis was obtained with the use of monofilament polypropylene sutures, Ligaclips (Johnson and Johnson, Cincinnati, Ohio, USA) and the Argon coagulator (Bard Electro Medical System, Inglewood, Colorado, USA). The CVP was monitored continuously from a zero point at mid-atrial level using a Hewlett Packard Anaesthetic Component Monitoring System (Medical Products Group, Andover, Massachusetts, USA). The CVP was measured as the mean CVP during liver parenchymal transection only, being a plateau in nearly all patients. None of the patients with a CVP greater than 5 cmH_2O had a fluctuation below this value. In eight patients the CVP was not measured for technical reasons. The blood loss was measured by the volume in the suction bottles combined with the increase in weight of the surgical packs. Patients were transfused perioperatively as indicated on clinical grounds to maintain a haemoglobin level above 10 g/dl.

Patients were analysed in two groups according to whether their CVP was greater or less than (or equal to) 5 cmH_2O. These groups were analysed with respect to blood loss and blood transfusion requirements. In the earlier part of the study one quarter of patients had a CVP of 5 cmH_2O or less, whereas in the latter part of the study, half had a CVP of 5 cmH_2O or below.

Statistical analysis

Comparisons of length of operation and number of lesions between the two CVP groups were made using the Mann–Whitney *U* test. Analysis of blood loss was performed on log transformed data. Changes in blood loss for the two levels of CVP in the two groups of portal occlusion and non-occlusion were analysed using regression techniques fitting an interaction between CVP and portal occlusion. A similar analysis was performed with an interaction between CVP and operation type. The factors that may have contributed to blood loss, presence or absence of portal occlusion, operation type, operating time, number of lesions resected, method of liver dissection and cirrhosis were analysed by analysis of variance (ANOVA).

Results

The median blood loss for all liver resections was 450 (range 25–8000) ml. Only two of the 40 patients with a CVP of 5 cmH_2O or less had a blood transfusion (500 ml, 1000 ml), while 25 of the 52 patients with a CVP greater than 5 cmH_2O required a blood transfusion (median transfusion 1500 (range 500–8000) ml). Blood loss and transfusion requirements were significantly less in patients with a CVP less than or equal to 5 cmH_2O during resection than in those with a pressure greater than 5 cmH_2O (*Table 2*). Possible confounding factors that may have contributed to blood loss were evaluated by ANOVA. These included the presence or absence of portal occlusion, the operation type, the operating time, the number of lesions resected, the method of liver dissection and cirrhosis.

Fig. 1 relates blood loss to CVP, with and without portal triad occlusion. Without portal triad occlusion the mean(s.e.) blood loss in patients with a CVP of 5 cmH_2O or less was 167(33) ml and in those with a CVP greater than 5 cmH_2O it was 1833(515) ml ($P<0{\cdot}001$). Similarly, with portal occlusion there was a significant difference in mean blood loss between the two groups: 400(126) and 1344(264) ml respectively ($P<0{\cdot}001$). An analysis of the effect of CVP within each type of liver resection for patients with and without cirrhosis, ultrasonic dissection or a clamp-fracture dissection technique and for the length of the operation showed a significant reduction in blood loss for all procedures in patients with a CVP less

Table 2 Comparison of blood loss and blood transfusion requirements in patients with a central venous pressure less than or greater than 5 cmH_2O

	Median blood loss (ml)	Blood transfusion (ml)	Total no. of patients	No. of patients transfused
CVP (cmH_2O)				
≤5	200	0–1000	40	2 (5)
>5	1000	0–8000	52	25 (48)
P	<0·0001	0·0008		

Values in parentheses are percentages. CVP, central venous pressure (Mann–Whitney *U* test)

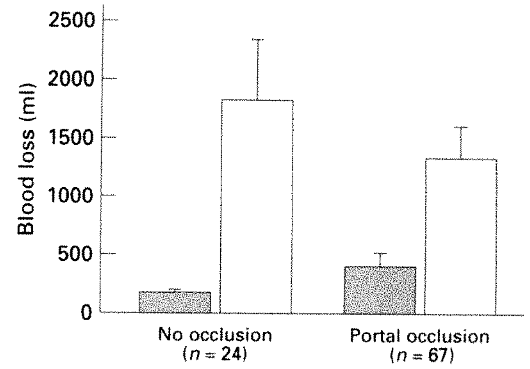

Fig. 1 Mean(s.e.) blood loss during liver resection with and without portal triad occlusion. There was a significant difference in blood loss between patients with a central venous pressure (CVP) greater than 5 cmH_2O (□) and those with a CVP of 5 cmH_2O or less (▨), both with and without portal occlusion ($P<0{\cdot}001$, Mann–Whitney *U* test)

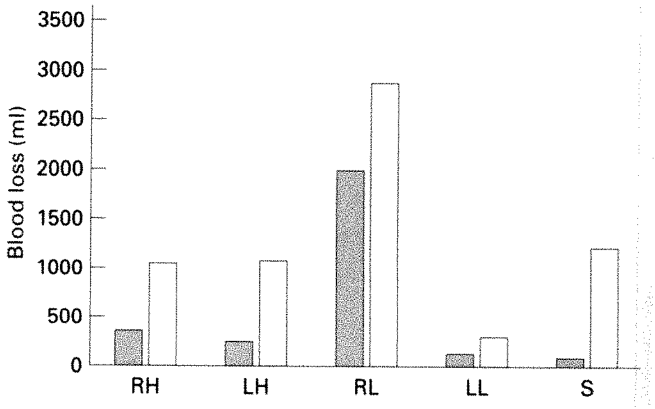

Fig. 2 Mean blood loss by operation type in patients with central venous pressure above 5 cmH_2O (□) and less than or equal to 5 cmH_2O (▨). There was significantly less blood loss in the latter patients for each type of liver resection except left lobectomy (LL; Couinaud segments II–III). RH, right hemihepatectomy (segments V-VIII); LH, left hemihepatectomy (segments II–IV); RL, right lobectomy (segments I, IV–VIII); S, segmentectomy or subsegmentectomy. $P<0{\cdot}05$ or better for RH, LH, RL and S (ANOVA)

than or equal to 5 cmH_2O (*Fig. 2*), significant for all operative types except left lobectomy where the numbers involved were too small to analyse.

Discussion

This study showed a significant reduction in blood loss and blood transfusion requirements in patients undergoing liver resection when the CVP was maintained at less than or equal to 5 cmH_2O during parenchymal dissection. This result was not influenced by the presence or absence of portal occlusion, the resection type, the length of operation, the number of lesions resected, the method of liver dissection or the presence or absence of cirrhosis. The principle of maintaining a low CVP to decrease blood loss has been alluded to in the literature[11-14], but until recently had little published support. A preliminary report showed a significant reduction in blood loss after instituting a 'low CVP' policy comparing patients studied with historical controls[14]. However, correction for other factors that may have influenced blood loss was not made, making a firm correlation of CVP to blood loss difficult. A study of 20 patients showed strong correlation between three bands of CVP (less than 6, 6–12, greater than 12 mmHg) and operative blood loss[15]. These authors did not examine other risk factors in their study.

The potential for air embolism, while maintaining a low CVP during division of the liver, is significant. A negative CVP can rapidly allow large volumes of air through small or unrecognized lacerations of the hepatic veins. This is unlikely with a positive CVP. Steps were taken to avoid an air embolus in this series by immediate oversewing of any holes in the hepatic veins during parenchymal dissection. For early recognition of air embolus, end-tidal carbon dioxide was monitored continuously. Any abrupt drop in end-tidal carbon dioxide would suggest air embolus, especially if associated with haemodynamic change. A minor fall in end-tidal carbon dioxide was common, but a small air embolism was suspected in only two patients.

The results of this study have altered the authors' practice of liver resection. The CVP during parenchymal resection is now kept between 2 and 5 cmH_2O, and patients are not fluid volume loaded at operation. A glyceryl trinitrate infusion is commenced at the start of the resection, to lower CVP if necessary, and can be continued throughout the liver parenchymal division phase. The patient is positioned head up or diuretics also used as required.

Maintaining a low CVP throughout hepatic resection reduces blood loss and blood transfusion requirements. This is particularly evident when the area of parenchymal resection is larger, such as a hemihepatectomy or non-anatomical resection. Lowering the CVP is a simple and effective way to reduce blood loss during liver surgery.

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Heat shock protein 72 production in liver tissue after experimental total hepatic inflow occlusion

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Background The pathogenesis of hepatic ischaemia–reperfusion injury is incompletely understood. This study examined the effects of reperfusion with congested portal blood on ischaemia–reperfusion injury of the liver following Pringle's manoeuvre, as monitored by heat shock protein (HSP) 72 production in rat liver tissue.

Methods Rats were randomized to three groups. In group 1 hepatic ischaemia with portal congestion was induced by Pringle's manoeuvre for 15 min; in group 2 Pringle's manoeuvre was applied for 15 min with an extracorporeal portasystemic shunt; and in group 3 the superior mesenteric vein was occluded for 15 min. The production of HSP72 in liver tissue was measured by Western blotting at 48 h after each intervention. Conventional parameters for hepatic function were examined at 1, 3 and 48 h after reperfusion.

Results There was marked HSP72 expression in group 1, but not in group 2 or 3, showing that a combination of liver ischaemia and reperfusion of congested portal blood is required to induce strong expression of HSP72 in the tissue. On the other hand, biochemical parameters were raised equally in both groups 1 and 2, reflecting a similar degree of ischaemic hepatocyte injury.

Conclusion The additional stress impact of temporary portal occlusion upon ischaemia–reperfusion injury of the liver was clearly detected by *in situ* hepatic HSP72 production in this study.

Application of Pringle's manoeuvre, with cross-clamping of the hepatoduodenal ligament, has been shown to reduce blood loss during hepatic parenchymal resection[1]. The disadvantage, however, is that prolonged total inflow occlusion may induce unwanted hepatocyte injury. It has been demonstrated repeatedly in the clinical setting that continuous Pringle occlusion in excess of 1 h, particularly where there is underlying cirrhosis, may induce profound hepatic dysfunction, with the induction of liver failure and death of the patient in some instances[2–6].

Although the pathogenesis of hepatic ischaemia–reperfusion injury after Pringle's manoeuvre is incompletely understood, there are three phases of injury: (1) hepatic ischaemia, (2) portal venous congestion and (3) reperfusion with arterial and congested portal blood. The reperfusion phase may be the dominant phase of injury. It has been revealed that reactive oxygen species and some chemical mediators activated during recirculation play an important role in the development of liver injury after ischaemia[7–10]. Prolonged occlusion of the portal system leads to marked congestion of the bowel wall, with breakdown of the intestinal barrier. Subsequent translocation of bacteria, or release of chemical inflammatory mediators or reactive oxygen species in portal blood, may be toxic to the liver. It is proposed that congested portal blood containing pathogens and activated inflammatory mediators may augment ischaemia–reperfusion injury of the liver. However, the specific roles of ischaemia, portal congestion and reperfusion have not been well documented in previous studies. Indeed, there is only indirect evidence to suggest a significant role for portal congestion in hepatic injury, as sensitive markers have not been available previously[11].

The discovery of the heat shock protein (HSP) gene family with its induction and hyperexpression after liver injury has been an exciting development in the science of liver injury. It was reported previously that HSP72 could be induced in liver tissue after normothermic ischaemia and reperfusion injury[12–14]. HSP72 is known to be one of the most fundamental stress proteins. The HSP70 gene family is highly conserved, present even in invertebrates, and is considered to be important in maintaining cellular homoeostasis and in increasing the chance of survival[15,16].

In the present study, the production of HSP72 was compared in three groups of rats, to determine the influence of hepatic reperfusion with congested portal blood on the development of ischaemia–reperfusion injury: (1) after 15 min of Pringle inflow occlusion and reperfusion with congested blood; (2) after a similar period of Pringle occlusion following creation of a temporary portasystemic shunt to prevent congestion; and (3) after 15 min of occlusion of the superior mesenteric vein only, without hepatic inflow occlusion, to determine the effects of portal congestion alone on the non-ischaemic reperfused liver.

Materials and methods

Male Wistar rats weighing 200–300 g were housed in an air-conditioned room (23–25°C) and exposed to 12-h light–dark cycles. Standard rat chow and water were provided *ad libitum*, according to the animal protection guidelines of Kyoto

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University. Rats were premedicated with intramuscular atropine sulphate injection (0·05 mg per kg body-weight) and anaesthetized with intraperitoneal pentobarbital sodium (40 mg per kg body-weight) for all operative procedures.

Rats were assigned randomly to three groups. In the first group (group 1), the abdomen was opened through a median laparotomy and the liver was detached from its ligaments. Total hepatic inflow occlusion with portal congestion was induced by clamping the hepatoduodenal ligament for 15 min with a microvascular clamp. Fifteen minutes of hepatic ischaemia was chosen for this study, since further prolonged periods of portal occlusion cannot be tolerated in the rat. In group 2, the abdomen was opened and the liver was mobilized in an identical manner. An extracorporeal portasystemic shunt was then created, by cannulating the caecal branch of the superior mesenteric vein and the external jugular vein, using polyethylene tubing (0·58 mm inner diameter, 200 mm long; Dural Plastics, Sydney, Australia) primed with 0·04 ml heparinized saline solution (250 units/ml). The liver was then exposed to a 15-min warm ischaemic insult by microvascular clamping of the hepatoduodenal ligament, but portal congestion was prevented by the extracorporeal shunt. In group 3, the abdomen was opened in an identical manner, and the superior mesenteric vein was occluded with a microvascular clamp for 15 min. Under these conditions, arterial and portal hepatic inflow from the splenic vein were maintained, and mesenteric congestion without hepatic ischaemia was achieved. During all the above interventions the abdomen was closed temporarily and an electric heating pad was placed beneath the animals to keep the rectal temperature at 35–37°C. Release of the microvascular clamp allowed immediate hepatic reperfusion, and blood and liver tissue samples were obtained at specified intervals.

For the detection of HSP72 production in the liver tissue at 48 h after each intervention, Western blot analysis was performed according to methods reported previously[17–19].

For the evaluation of tissue adenosine 5′-triphosphate (ATP) levels, liver tissue was sampled by freeze-clamping at 1 h ($n = 6$), 3 h ($n = 6$) and 48 h ($n = 6$) after reperfusion. Samples of frozen tissue (approximately 400 mg) were stored in liquid nitrogen pending assay. Each sample was homogenized with 2 ml of perchloric acid 0·33 mmol/l and the extract was centrifuged. The supernatant was neutralized with 69 per cent potassium carbonate solution (pH 5·5–6·0) and centrifuged again. Adenine nucleotide levels were assayed enzymatically in the supernatant[20,21]. Blood samples were taken from the aorta at 1 h ($n = 6$), 3 h ($n = 6$) and 48 h ($n = 6$). The serum concentrations of alanine aminotransferase (ALT) and lactic dehydrogenase (LDH) were assayed on a standard biochemistry autoanalyser. After sampling, rats were killed humanely under anaesthetic.

Values are expressed as mean(s.d.). Statistical analysis was performed by one-factor analysis of variance (ANOVA) with Bonferroni/Dunn *post hoc* comparisons. $P < 0·05$ was considered to be significant.

Results

The accumulation of inducible HSP72 in rat liver tissue after 48 h of reperfusion in each group is shown in *Fig. 1*. In normal liver tissue and tissue from group 3, HSP72 was not detectable. In groups 1 and 2, where rats were subjected to hepatic ischaemia, HSP72 was induced. HSP72 was markedly overexpressed in group 1 but its accumulation in group 2 was minimal.

Changes in ATP concentration in the liver tissue at 1, 3 and 48 h after reperfusion are shown in *Fig. 2*. The ATP levels in groups 1 and 2 were significantly lower than those in group 3 at 1 and 3 h after reperfusion but there were no differences between groups 1 and 2. At 48 h after reperfusion, there were no significant differences between the three groups.

Changes in serum ALT and LDH levels in each group are shown in *Fig. 3*. At 1 h after reperfusion, ALT levels in groups 1 and 2 rose to over 4000 units/l, while the mean value in group 3 was 300 units/l, significantly lower than that in group 1 or 2. At 3 h after reperfusion, ALT concentration in group 1 remained raised, but levels in groups 2 and 3 recovered to 2700 and 200 units/l respectively. LDH levels increased to 40 000 units/l in both groups 1 and 2, but the mean value in group 3 was less than 10 per cent of that in groups 1 and 2. The pattern of LDH increase after reperfusion was similar to that of ALT.

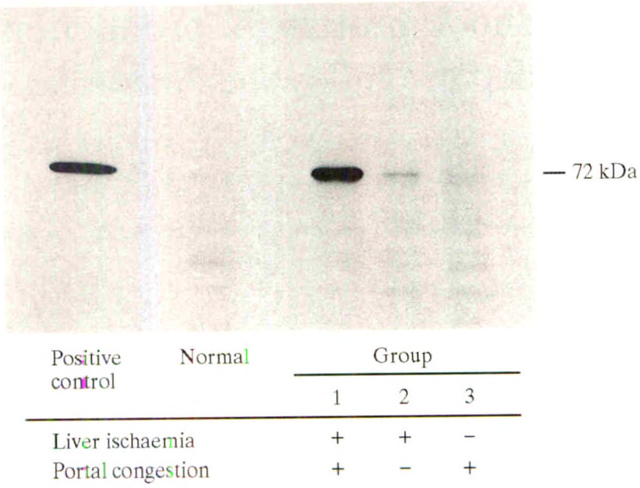

Fig. 1 Heat shock protein (HSP) accumulation in the rat liver after 48 h of reperfusion in each group compared with that in normal liver (5 μg protein per lane). HSC70, which contains inducible HSP72 in approximately 10 per cent, was used as a positive control (0·2 μg per lane)

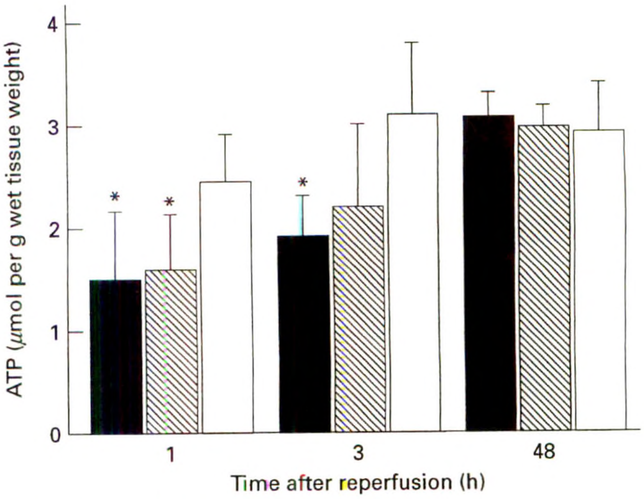

Fig. 2 Changes in adenosine 5′-triphosphate (ATP) concentration in liver tissue at 1, 3 and 48 h after reperfusion in groups 1 (■), 2 (▨) and 3 (□). Values are expressed as mean(s.d.). The ATP levels in groups 1 and 2 were significantly lower than that of group 3 at 1 h after reperfusion (group 1 *versus* group 3: $F = 4·90$, 15 residual d.f., $P = 0·02$ (analysis of variance (ANOVA)); $P = 0·01$ (*post hoc* comparison)) and at 3 h after reperfusion (group 1 *versus* group 3: $F = 5·59$, 15 d.f., $P = 0·02$ (ANOVA); $P = 0·01$ (*post hoc* comparison)), but there were no differences between groups 1 and 2 (1 h, $P = 0·75$; 3 h, $P = 0·41$). At 48 h after reperfusion, there were no significant differences between the three groups ($F = 0·26$, 15 d.f., $P = 0·78$). $^*P < 0·05$ *versus* group 3 (ANOVA)

In the comparison between ALT and LDH levels in groups 1 and 2, there was a trend towards higher transaminase levels in group 1 but it was not statistically significant (ALT: 1 h, $P=0{\cdot}46$; 3 h, $P=0{\cdot}05$. LDH: 1 h, $P=0{\cdot}31$; 3 h, $P=0{\cdot}16$). By 48 h, ALT and LDH levels were no different between the groups (ALT: group 1, 226(155) units/l; group 2, 181(103) units/l; group 3, 66(36) units/l; $F=3{\cdot}43$, 15 d.f., $P=0{\cdot}06$. LDH: group 1, 588(265) units/l; group 2, 476(248) units/l; group 3, 450(302) units/l; $F=0{\cdot}43$, 15 d.f., $P=0{\cdot}66$).

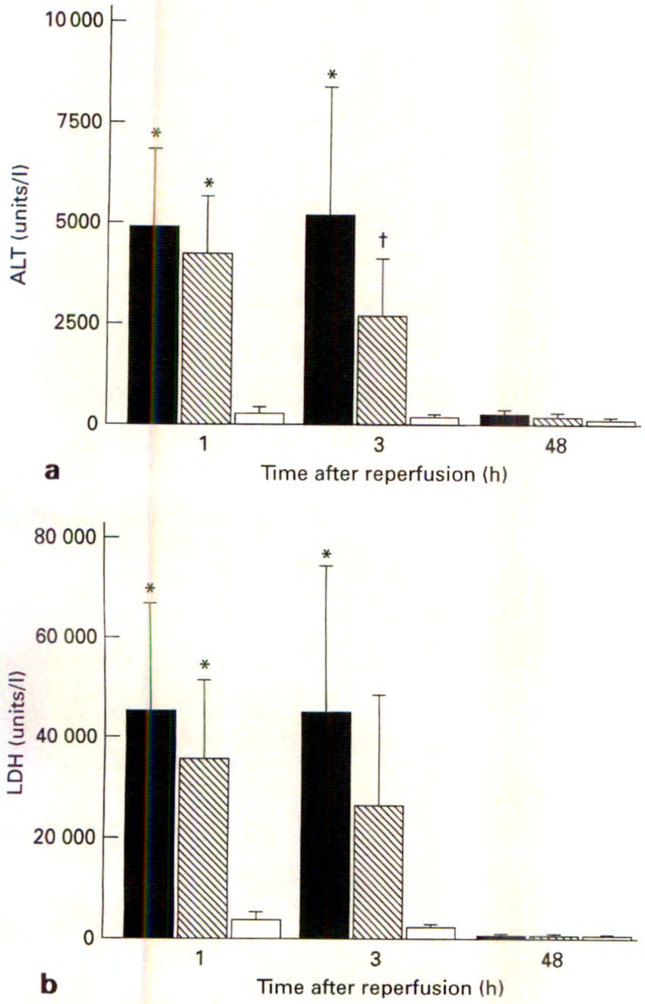

Fig. 3 Changes in **a** serum alanine aminotransferase (ALT) level and **b** serum lactate dehydrogenase (LDH) level at 1, 3 and 48 h after reperfusion in groups 1 (■), 2 (▨) and 3 (□). Values are mean(s.d.). At 1 h after reperfusion, the ALT level in groups 1 and 2 increased significantly more than that in group 3 ($F=17{\cdot}90$, 15 d.f., $P<0{\cdot}001$ (analysis of variance (ANOVA)); $P<0{\cdot}001$ (group 1 *versus* group 3), $P<0{\cdot}001$ (group 2 *versus* group 3) (*post hoc* comparison)). At 3 h after reperfusion, ALT concentration in group 1 remained raised, but levels in groups 2 and 3 decreased ($F=9{\cdot}05$, 15 d.f., $P=0{\cdot}003$ (ANOVA); $P<0{\cdot}001$ (group 1 *versus* group 3), $P=0{\cdot}05$ (group 2 *versus* group 3) (*post hoc* correction)). LDH levels also increased remarkably in both groups 1 and 2, but mean values in group 3 were less than 10 per cent of those in groups 1 and 2 ($F=11{\cdot}82$, 15 d.f., $P<0{\cdot}001$ (ANOVA); $P<0{\cdot}001$ (group 1 *versus* group 3), $P=0{\cdot}003$ (group 2 *versus* group 3) (*post hoc* correction)). The pattern of LDH increase after reperfusion was similar to that of ALT (at 3 h of reperfusion: $F=6{\cdot}00$, 15 d.f., $P=0{\cdot}01$ (ANOVA); $P=0{\cdot}004$ (group 1 *versus* group 3), $P=0{\cdot}07$ (group 2 *versus* group 3) (*post hoc* correction)). $^*P<0{\cdot}01$, $^\dagger P<0{\cdot}05$ *versus* group 3 (ANOVA)

Discussion

HSP72 is an ubiquitous protein, highly conserved throughout the evolutionary scale, which has been shown to be induced rapidly in response to stress. It appears to be an important adaptational response to hibernation, and is believed to constitute an endogenous protective response to injury. Blockade of this pathway has been shown to augment susceptibility to hypoxic injury[22]. Ischaemic preconditioning of tissue and organs, with short periods of ischaemia preceding the final insult, has been shown to protect cells from injury, and a likely mechanism of protection includes HSP72 induction. Hyperexpression of HSP72 has been shown to protect cultured neurones from heat shock[23], and may decrease cardiac infarct size in mouse models of myocardial ischaemia[24]. Regulation of HSP72 production is mediated via activation and binding of a heat shock transcription factor to a specific sequence of the promoter, called the heat shock element[25]. It was previously shown that HSP72 induction by heat stress was able to protect significantly against subsequent warm ischaemic liver injury in the rat[26].

The present study addressed the role of reperfusion of the ischaemically injured liver with congested portal blood after temporary Pringle inflow occlusion. It was hypothesized that portal congestion, with its potential for induction of bacterial translocation, endotoxin and other immune activation pathways, may constitute a 'second-hit' insult to the ischaemically injured liver. Intrahepatic production of HSP72 was used as a highly sensitive indicator of liver injury in this study.

A limited period of 15 min of total hepatic inflow occlusion (group 1) caused marked serum increases in ALT and LDH levels at 1 and 3 h after reperfusion, which returned to baseline within 48 h of surgery, indicating that significant, but reversible, hepatocellular injury had been induced. Creation of a temporary portasystemic shunt to relieve portal congestion followed by Pringle occlusion (group 2) also led to marked increases in ALT and LDH levels, with a non-significant trend toward lower transaminase levels compared with group 1. Intrahepatic stores of ATP were reduced similarly early after injury, with complete recovery by 48 h.

In terms of HSP72 induction, there was high expression in the livers of group 1 animals, where ischaemic injury was followed by reperfusion with congested portal blood. Where a portasystemic shunt was used, however, there was minimal HSP72 expression at 48 h. It would appear from the data, therefore, that a limited period of 15 min of warm ischaemia followed by hepatic reperfusion with non-congested portal blood was an inadequate stimulus for HSP72 synthesis in the rat liver. In contrast, Tacchini *et al.*[27] reported that inflow occlusion of the partial liver for the longer period of 60 min induced the expression of HSP70 messenger RNA (mRNA) in the ischaemic lobe of rat livers. In their experiment, portal circulation to the non-ischaemic liver lobes was maintained during hemiocclusion of the hepatic inflow and portal congestion was therefore avoided. Nevertheless, the stress response was triggered only by ischaemia. It would appear that, in the absence of portal congestion, marked HSP72 induction occurs only when severe parenchymal damage has been initiated by prolonged ischaemia.

The present study has demonstrated an important synergistic interaction of congested portal blood reperfusion and as little as 15 min of Pringle-induced ischaemia on the production of HSP72 in liver tissue. Schoeniger *et al.*[13] reported that activation of HSP72 gene transcription in porcine liver after Pringle-induced ischaemia did not occur until after restoration of blood flow. They showed that the reperfusion phase led to maximal transcription of HSP72 mRNA, which was found to be highly dependent on the generation of superoxide anions. Although this report suggests the importance of reperfusion injury in the stress response of the liver after ischaemia, the role of portal blood pooling during reperfusion was not addressed specifically. The aetiological mechanism of ischaemic injury synergy with congested portal blood is presumed to be complex and multifactorial. It is likely that pathogen translocation, endotoxin release and immune activation may all play a part in exacerbating ischaemia–reperfusion injury in the liver. A key intermediate may be production of reactive oxygen species in portal blood after oxidative stress, which is known to activate the heat shock response[28,29]. Free radical generation in portal blood during portal occlusion may be particularly harmful to the ischaemically injured liver during reperfusion. Increased xanthine oxidase activity in the portal plasma and increased permeability of the small intestinal wall may be other factors leading to heightened injury after ischaemia and reperfusion[7]. Moreover, bacterial translocation caused by congestion of the portal vein leads to release of both endotoxin and a variety of cytokines[9], which may also cause HSP induction, as speculated by some authors[16,30–33]. Results for the control group (group 3), in which superior mesenteric occlusion was induced in the absence of liver ischaemia, clearly indicated that hepatic perfusion with portal toxins alone was insufficient to induce HSP72 production.

The present study has demonstrated that HSP72 might prove to be a more useful marker than transaminase release or hepatic ATP content in evaluating the degree of hepatic injury after ischaemia–reperfusion. A drawback of HSP72 monitoring is that *de novo* synthesis may limit assessment of dynamic changes in acute liver injury. To overcome this shortfall, examination of HSP72 mRNA may be of more relevance in clinical applications.

Although a 15-min Pringle's manoeuvre is not fatal for Wistar rats, the stress response induced by reperfusion with congested portal blood was a highly potent stimulator of HSP72 production compared with non-congested reperfusion. More prolonged periods of inflow occlusion may cause further accumulation of pathogens in the portal system leading to fulminant liver failure and early death in the rat. The failure of intermittent portal triad cross-clamping in protection from injury was confirmed by analyses of arterial ketone body ratio and liver-related enzyme levels in serum[11]. According to differences in mechanisms of stress response with HSP72 synthesis, alteration in mitochondrial energy status of hepatocytes, and liberation of liver enzymes into serum during and after ischaemia–reperfusion, HSP72 synthesis seems to be an early event in cellular dysfunction and its action may be more sensitive to this type of injury than arterial ketone body ratio or conventional parameters of liver damage.

In conclusion, the deleterious effect of warm ischaemia–reperfusion in the liver tissue induced by short-term Pringle's manoeuvre was attributable principally to synergistic toxicity from reinflow of congested portal blood. The influence of congested portal blood on ischaemia–reperfusion injury was detected clearly using HSP72, which is now advocated as a highly sensitive parameter of injurious stress to the liver.

Acknowledgements

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Short note

Prospective randomized trial of 5- and 10-mm epigastric ports in laparoscopic cholecystectomy

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Laparoscopic cholecystectomy has traditionally been undertaken with two 10-mm ports, one at the umbilicus and the other in the epigastrium. Two further 5-mm ports are placed along the line of a Kocher's incision. There has been a recent drive to reduce port sizes first with the introduction of a 5-mm laparoscope and then with equipment designed for 3- and 2-mm port sizes[1,2]. Unlike the introduction of new medication[3], many variations in surgical technique are introduced without a prospective randomized controlled trial to assess their efficacy. There appear to be theoretical reasons why reducing port sizes might reduce pain and speed recovery after laparoscopic cholecystectomy. A prospective randomized trial has therefore been conducted to assess the impact on patients of reducing the epigastric port size to 5 mm.

Patients and methods

Over a 4-month period, 60 consecutive patients were invited to be randomized to either traditional '10-mm' laparoscopic cholecystectomy or '5-mm' laparoscopic cholecystectomy. Patients in the 5-mm group had the cystic duct secured with a 5-mm clipper (Ethicon, Cincinnati, Ohio, USA) and the gallbladder removed from the umbilicus under direct vision using a 5-mm, 30° laparoscope (KeyMed, Southend-on-Sea, UK), placed in the epigastric port. Standard dressings were applied at the end of operation to ensure that ward staff could not differentiate between the two groups. Patients received a standardized anaesthetic and a record was kept of total morphine consumption, and pain scores at 1, 3, 6 and 18 h after surgery. Discharge from hospital and date of return to normal activity or work was also recorded. All data were collected by the first two authors without prior knowledge of which operation had been undertaken.

Results

Of 60 patients approached, three refused to take part in the study. Four further patients refused to have pain scored after operation. Of 53 remaining patients, 26 underwent 10-mm laparoscopic cholecystectomy and 27 5-mm laparoscopic cholecystectomy. The results are shown in *Table 1*. There were no significant differences in any of the variables measured. Complications occurred in five patients in the 5-mm group; four required conversion to more than one 10-mm port because of dense adhesions and thick-walled gallbladders while one patient in this group required conversion to open surgery. There were no wound infections requiring antibiotics or hernias in either group during the 6 months after surgery.

Table 1 Age, duration of operation, pain scores, analgesia consumption, hospital stay and return to work after 5-mm and 10-mm laparoscopic cholecystectomy

	10 mm	5 mm	P*	95% confidence interval
Age (years)	58 (30–80)	52 (28–73)	n.s.	—
Duration of operation (min)	70 (43–108)	73 (33–125)	0·86	−13 to 13
Pain score				
1 h	3·2 (0–9·9)	3·0 (0–9·9)	0·87	−1·8 to 1·5
3 h	3·2 (0–9·9)	3·0 (0–7·0)	0·47	−2 to 1
6 h	2·0 (0–9·9)	3·0 (0–8·0)	0·15	−2 to 0·1
18 h	3·0 (0–5·0)	1·0 (0–7·8)	0·17	5 to −2
Total morphine (mg)	10 (0–34)	10 (0–46)	0·58	−6 to 5
Hospital stay (h)	24 (14–72)	24 (17–72)	0·97	−6 to 5
Time to return to normal (days)	4 (1–14)	3 (1–7)	0·19	−6 to 4

Values are median (range). n.s., Not significant. *Mann–Whitney *U* test

Discussion

Laparoscopic cholecystectomy is inherently a procedure associated with a short hospital stay and low pain scores in the postoperative period. Significant improvement in pain scores and a reduction in opiate usage can be achieved by using diclofenac sodium[3]. This prospective randomized study has failed to show any significant benefit in postoperative pain, opiate consumption or return to normal activity as a result of a reduction in the epigastric port size from 10 to 5 mm. Power calculations based on previous work[3] had suggested that this sample size would be large enough to detect significant changes in pain scores or analgesic requirements.

It is highly likely that at least one 10-mm port will be required for laparoscopic cholecystectomy in the UK, so that thick-walled and stone-laden gallbladders may be removed from the peritoneal cavity. This being so, then the first choice for reducing port sizes would be the 10-mm epigastric port. Reduction in size avoids the need for suture closure of the deep fascia in the epigastrium and may have some cosmetic benefits. It does not, however, have significant clinical benefits in terms of pain relief or analgesia consumption. Pressure to further reduce port sizes to 2 or 3 mm should be resisted unless there is objective clinical benefit, particularly as instruments designed for such ports are not as effective for handling severely diseased gallbladders as 5- or 10-mm instruments (personal observation). If additional expense is involved in the reduction in port sizes (which was not the case in this study), or if instrument effectiveness is

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compromised in a drive for ever smaller ports, there should be objective benefits to the patient in terms of postoperative pain and overall recovery before a change to smaller ports can be recommended.

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Surgical treatment of 32 patients with peripheral intrahepatic cholangiocarcinoma

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Background Peripheral intrahepatic cholangiocarcinoma (PIC) is an intrahepatic primary liver neoplasm which is clinicopathologically distinct from hepatocellular carcinoma and major duct cholangiocarcinoma. The clinical outcome after resection of these rare tumours is not well documented.

Methods Review of the hepatic database and tumour registry at Memorial Sloan-Kettering Cancer Center identified 32 cases of PIC resected for cure over a 23-year period. Intrahepatic cholangiocarcinomas with major bile duct involvement were excluded from this analysis. Demographics, pathological features, biochemical markers, operative results and survival were analysed.

Results The majority of patients presented with abdominal pain ($n = 19$). Only two patients had pathological evidence of hepatic cirrhosis. Serum marker levels included α-fetoprotein (AFP; median 3·7 (range 0–225) ng/ml) and carcinoembryonic antigen (CEA; median 1·6 (range 0–30) ng/ml). Type of hepatic resection included: wedge ($n = 2$), lobectomy ($n = 14$) and extended lobectomy ($n = 16$). There was one postoperative death. Median follow-up time was 27 months. Median survival was 59 months with an actuarial 5-year survival of 42 per cent. Vascular invasion and intrahepatic satellite lesions were predictors of worse survival ($P < 0·05$).

Conclusion PIC is a rare hepatic primary tumour, which usually presents in non-cirrhotic livers with a normal serum AFP and CEA level. In selected patients, complete surgical resection can be performed safely and is associated with long-term survival.

Bile duct tumours include a spectrum of diseases defined by location and histology. Cholangiocarcinomas may arise in the distal extrahepatic bile ducts, proximal intrahepatic major ducts (Klatskin tumours), as well as from peripheral intrahepatic biliary radicals. Each location has its own presentation and natural history. In addition to prognosis, distinction between the three tumour sites is important in terms of treatment planning. The surgical option for distal cholangiocarcinomas is usually pancreaticoduodenectomy[1]. For proximal or hilar bile duct lesions, major bile duct excision with or without hepatic resection is indicated[2]. For peripheral intrahepatic cholangiocarcinoma (PIC), hepatic resection is usually indicated, occasionally requiring extrahepatic bile duct excision for complete tumour clearance[3].

Of the three, PIC is the least common and has been referred to by a variety of terms including cholangiocellular carcinoma, cholangiolar carcinoma or peripheral cholangiocarcinoma. Although rare, PIC is the second most common hepatic primary tumour after hepatocellular carcinoma. Pathologically, these tumours represent a transition from hepatocellular to extrahepatic cholangiocarcinoma. Importantly, PIC is clinicopathologically distinct from hepatocellular carcinoma and major duct cholangiocarcinoma, and the clinical outcome after resection of these rare tumours is not well documented. The current paper reports 32 patients with PIC who underwent surgical resection at a tertiary referral centre, in order to define perioperative results and to identify predictors of long-term survival.

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Patients and methods

Review of the authors' prospective hepatic database and tumour registry identified 32 cases of PIC resected for cure over a 23-year period. Patients were selected based on the absence of extrahepatic disease and technical ability to undergo resection. Postoperative chemotherapy was not administered routinely. Intrahepatic cholangiocarcinomas with any major bile duct involvement were excluded from this analysis. All pathological specimens were reviewed to confirm the diagnosis of PIC. Tumours with minimal hepatocellular features were included (PIC, mixed type; $n = 3$). Tumours were classified according to the criteria of the American Joint Commission on Cancer[4].

A right lobectomy included resection of hepatic segments V, VI, VII and VIII. The inclusion of segment IV in the resected specimen constituted an extended right lobectomy (right trisegmentectomy). A left lobectomy included segments II, III and IV, and the addition of segments V and VIII was defined as an extended left lobectomy (left trisegmentectomy).

Medical records were reviewed and the following factors were analysed: (1) demographics, (2) symptoms at presentation, (3) biochemical markers and (4) intraoperative factors, including operative time, blood loss and transfusion requirements. Outcome measures included length of hospital stay, operative deaths and overall survival.

Data are expressed as median (range). Survival was calculated by the Kaplan–Meier method and compared by log rank test with statistical significance defined as $P < 0·05$.

Results

Patient characteristics

Thirty-two patients underwent resection for PIC (five from 1972 to 1987, six from 1988 to 1991 and 21 cases from 1992 to 1995). There were ten men and 22 women of median age 69 (49–82) years. None of the patients presented with intrahepatic stones or parasitic infections. The most common symptom at presentation was abdominal pain ($n = 19$). Only one patient presented with jaundice. Eight patients had a history of hepatitis. There were equal numbers ($n = 12$) of primary tumours in the right and left lobes. Eight patients presented with tumours involving both lobes.

The majority of patients presented with serum bilirubin levels within the normal range (0–1 mg/dl), with a median value of 0·5 (0·3–18·3) mg/dl. Serum α-fetoprotein (AFP; normal range 0–10 ng/ml) levels were raised in four of 20 patients (median 3·7 (0–225) ng/ml). Carcinoembryonic antigen (CEA; normal range 0–5 ng/ml) levels were raised in two of 18 patients (median 1·6 (0–30) ng/ml).

Operative results

Of the 32 patients, two underwent wedge resection, 14 underwent lobectomy and 16 patients required an extended hepatic lobectomy (trisegmentectomy) for tumour clearance. All resections were macroscopically complete. The median operating time was 4·5 (2·3–8·5) h. The median operative blood loss was 1000 (200–5900) ml and median blood transfusion was 2 (0–11) units of packed red blood cells. One patient died 14 days after operation from sepsis. The median hospital stay was 11 (3–81) days.

Pathology

The median tumour size was 8·0 (3–16) cm. Four patients had positive lymph nodes. Resection margins were positive in six patients. Satellite lesions were detected in 13 patients, perineural invasion in seven and vascular invasion in ten patients. Only two patients had pathological evidence of cirrhosis. Microscopic vascular invasion correlated with the presence of intrahepatic satellite metastasis ($P < 0·005$, χ^2 test).

Survival

Median follow-up for the entire cohort was 27 (4–117) months. Median survival was 59 months with a projected 5-year survival of 42 per cent (*Fig. 1*). Patients with stage II disease ($n = 16$) did significantly better (median survival 63 months) than patients with stage III tumours ($n = 15$; median survival 20 months) ($P < 0·02$). All four patients with positive nodal disease died; one from perioperative complications and the remaining three from recurrence at 6, 8 and 19 months. Vascular invasion and intrahepatic satellite lesions were predictors of worse survival ($P < 0·05$). Patients with positive resection margins ($n = 6$) had a worse median survival (9 months) than those with negative margins (63 months). Sex, age, perineural invasion and tumour site did not correlate with outcome.

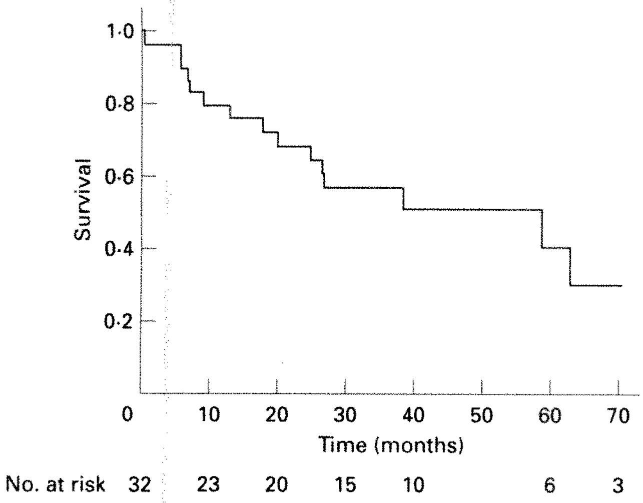

Fig. 1 Overall survival for patients undergoing resection for peripheral intrahepatic cholangiocarcinoma. Median survival was 59 months

Discussion

PIC is a relatively rare primary hepatic tumour, which is clinically distinct from hepatocellular carcinoma and extrahepatic cholangiocarcinoma. The majority of patients with hepatocellular carcinoma present with cirrhosis and raised serum AFP levels, whereas patients with perihilar or distal cholangiocarcinomas present with jaundice. In contrast, patients with PIC usually present with abdominal pain in the absence of jaundice, associated with a non-cirrhotic liver and normal serum AFP and CEA levels.

Similar to other Western reports[5], this series did not identify any risk factors associated with PIC. This is different from Asian series, which report an association with liver fluke infestation and hepatolithiasis[6–8]. This report also demonstrates that resection can be performed safely with an operative mortality rate of 3 per cent (one of 32 patients). This is similar to this institution's perioperative mortality rate for hepatic resection for non-cirrhotic hepatocellular carcinomas and metastatic tumours[9].

The overall median survival of 59 months for this series is significantly longer than that in other reported studies[3,5,8,10,11]. This improved survival is likely to be the result of patient selection. Patients with major bile duct involvement were excluded to ensure that patients with hilar cholangiocarcinomas were not included in this study. Some series include these patients, which might account for a worse survival rate[5,10,12]. The improved outcome in the present series may be explained by the early stage distribution; approximately half of the patients presented with stage II disease (node negative, no vascular invasion) and, in contrast to other reports[3,5], no patients with stage IVa disease in this cohort were resected. This early stage distribution most likely represents a combination of referral bias, as well as a selection bias by the surgeon.

In addition to stage, the presence of intrahepatic satellite lesions or vascular invasion predicted a worse outcome in this study. Interestingly, there was a significant correlation between microscopic vascular invasion and the presence of intrahepatic satellite metastasis. This association has also been described by others and has been suggested to be a factor contributing to the high incidence of early intrahepatic and extrahepatic metastasis associated with PIC[13]. Yamamoto *et al.*[12] reported that 60 per cent of resected PICs had evidence of vascular involvement and, of these, 83 per cent had intrahepatic metastasis; of the remaining lesions without vascular invasion, none had intrahepatic satellites.

The ability to obtain clear surgical margins also affected outcome. Six of the present patients had microscopically positive surgical margins, which translated into a worse median survival (9 months) compared with that of those with negative margins (63 months). Other series reported 26–36 per cent margin positivity rates[7,10], which also correlated with survival. This high rate of margin positivity may be explained by the fact that many patients present late, with large tumours often involving both lobes (eight of 32 in this series). In addition, 13 of 32 tumours demonstrated multicentricity. In an attempt to perform a more encompassing resection, many groups have reported hepatic transplantation for PIC. Results so far have been disappointing, and many centres now consider PIC a contraindication for transplantation[3,14].

The presence of hilar lymph node metastasis is associated with a worse survival. Only four patients had documented positive lymph nodes, all of whom died from either postoperative complications ($n = 1$) or recurrent tumour ($n = 3$). The poor prognosis of patients with lymph node metastasis has been documented by others. Chou *et al.*[7] reported a 0 per cent 1-year survival of patients with positive lymph nodes resected for PIC ($n = 11$). This was significantly worse than that for those with negative lymph nodes ($n = 8$), with a 3-year survival of 64 per cent. Pichlmayr *et al.*[3] also noted a worse survival for patients with node-positive disease who had a median survival of 7·7 months compared with 21·2 months for patients with node-negative tumours.

In summary, the results of surgical resection for PIC at a single tertiary care cancer centre are reported. PIC is usually associated with non-cirrhotic livers in the face of normal serum AFP and CEA levels. In selected patients, complete surgical resection can be performed safely and is associated with long-term survival. Stage, margin status, microvascular invasion and the presence of intrahepatic satellite lesions predict outcome. Data from other institutions provide discouraging results of hepatic transplantation for these patients, and the only curative option at the present time is complete surgical resection.

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Contribution of computed tomography to decision making in the management of adhesive small bowel obstruction

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Background In adhesive small bowel obstruction, the early recognition of complications such as strangulation or volvulus is essential to choose between surgical or conservative initial treatment. The objective of this study was to determine prospectively the contribution of computed tomography (CT) to decision making in the management of these patients.

Methods Patients with suspected adhesive small bowel obstruction had CT at admission. Patients with CT signs of volvulus or strangulation and/or clinical signs of peritoneal irritation underwent urgent surgery; other patients had conservative initial treatment.

Results Fifty-four patients were evaluated. CT demonstrated signs of strangulation or volvulus in 19 patients, including three with signs of peritoneal irritation. Within this group, urgent laparotomy was performed in 17 patients and confirmed the CT diagnosis in 16. Thirty-seven patients without clinical or CT signs of complications had initial conservative treatment; among them, seven of 12 with a distal obstruction determined by CT required a delayed operation for persisting obstruction, compared with two of 25 patients with a proximal obstruction ($P < 0.01$).

Conclusion CT is useful for the evaluation of adhesive small bowel obstruction, to detect accurately patients with complications who require urgent operation and to determine the location of the adhesion, which represents a significant prognostic factor for success of conservative treatment

Conflicting opinions still exist about the choice between non-operative or surgical initial treatment for patients with adhesive small bowel obstruction (ASBO). This controversy is mainly related to the inability to differentiate accurately at an early stage strangulation from simple obstruction using conventional clinical criteria, plain abdominal radiography or laboratory data[1–4]. While successful conservative treatment has been reported[3,5,6], many authors recommend systematic early surgical exploration for all patients with ASBO to avoid excessive morbidity and mortality that may result from delayed operation[1,2,7].

Computed tomography (CT) has been advocated recently as a valuable procedure to evaluate ASBO. CT is able to diagnose the obstruction, its cause and location, and also to detect early signs of strangulation[8–13]. Moreover, CT may demonstrate the presence of volvulus secondary to adhesions, a condition that often leads to intestinal ischaemia or infarction[9,14,15].

The aim of the present study was to evaluate prospectively the contribution of CT to decision making in the management of patients with ASBO, first to detect at early stages the patients with complications, strangulation or volvulus, who have to be operated on as an emergency, and second to identify factors that may predict the success or failure of conservative treatment in patients with simple obstruction.

Patients and methods

From January 1995 to June 1997, all patients who presented with clinical symptoms of intestinal obstruction were candidates for inclusion in the study. Patients with an obstruction occurring in the month following an abdominal operation were excluded. Clinical evaluation consisted of physical examination, plain abdominal radiography and blood tests. As reported previously[1], the diagnosis of a strangulated occlusion was suggested clinically only by the presence of signs of peritoneal irritation. In contrast to partial obstruction, the diagnosis of complete obstruction was made at admission in cases of total constipation and when gas was absent in the colon on a plain abdominal radiograph.

All the patients had CT at admission, using a modern CT unit (Somatom Plus 4 A or C; Siemens Medical System, Erlangen, Germany); CT findings were interpreted independently from clinical data. On CT, the obstruction was demonstrated by the presence of dilated small bowel proximal to a transition zone and a collapsed distal small intestine or ascending colon. The diagnosis of ASBO was retained when no cause of obstruction could be identified at the level of the transition zone. The location of the obstruction, proximal or distal, was determined by the site of the transition zone. Based on the authors' experience and previous reports in the literature[10–13], the CT signs evaluated for the diagnosis of strangulation were: presence of ascites, presence of mesenteric congestion or intramesenteric fluid, wall thickening (bowel wall greater than 2 mm) and reduced mural enhancement after intravenous injection of contrast. This last sign was demonstrated by asymmetric enhancement in similarly distended adjacent loops, decreased in strangulated compared with non-strangulated bowel (*Fig. 1*). CT suggested the diagnosis of strangulation when reduced mural enhancement was demonstrated or when at least two of the other severity signs evaluated (ascites, mesenteric congestion, intramesenteric fluid or wall thickening) were present. Volvulus was diagnosed on CT if one of two signs was present: the whirl sign[16], corresponding to a whirlpool arrangement of the mesentery around the point of bowel torsion, and the abnormal distribution of the intestine with a fixed radial disposition of dilated bowel loops converging toward the point of torsion[14] (*Fig. 2*).

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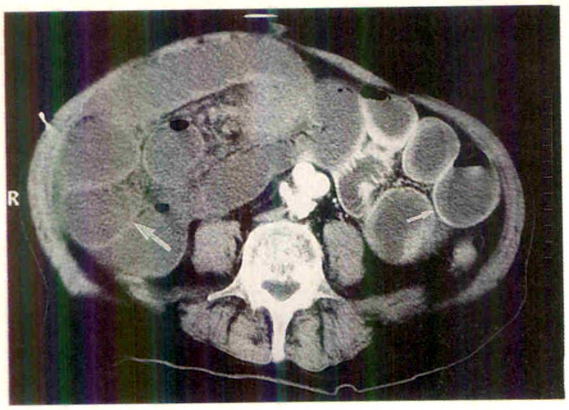

Fig. 1 Computed tomography after contrast injection, in a patient without signs of peritoneal irritation at admission, showed reduced mural enhancement (large arrow) in strangulated bowel loops compared with normal enhancement in similarly distended non-strangulated bowel (small arrow). Bowel ischaemia was confirmed at laparotomy and an intestinal resection of 180 cm was performed

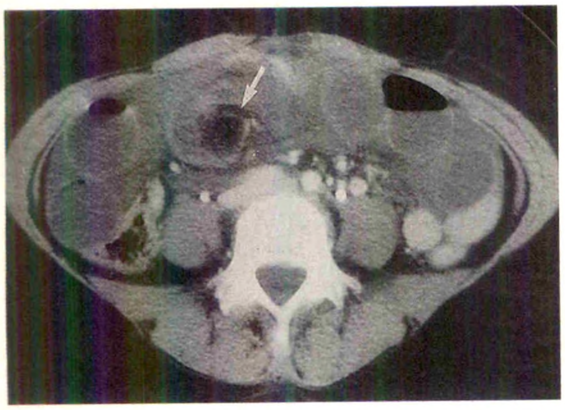

Fig. 2 Computed tomography at admission, in a patient without signs of peritoneal irritation, demonstrated a typical image of volvulus characterized by the presence of the whirl sign (arrow), consisting of a whirlpool arrangement of the mesentery around a central collapsed loop. Laparotomy confirmed the presence of a volvulus with secondary intestinal necrosis which required intestinal resection of 200 cm

After initial clinical and CT evaluation, all patients with a diagnosis of ASBO were included in the study. Two groups of patients were identified: patients with a suspicion of complicated obstruction, including those with clinical signs of peritoneal irritation and/or those with CT signs of strangulation or volvulus, and patients with a suspicion of simple ASBO with no clinical or CT signs of complication. Patients with suspected complicated ASBO underwent urgent laparotomy and those with a suspected simple obstruction were initially treated conservatively, using nasogastric decompression and administration of intravenous fluids. For patients treated conservatively, delayed laparotomy was decided upon when clinical conditions deteriorated or did not improve within 72 h. The final diagnosis was made at the end of the evaluation. The diagnosis of complicated obstruction was always established at laparotomy, when macroscopic signs of intestinal ischaemia and/or a volvulus of the bowel of at least 180° around the mesenteric vessels were observed. The diagnosis of simple ASBO was retained in patients relieved with non-operative therapy and in those whose operation did not reveal any ischaemic lesions or volvulus.

For each patient, initial clinical and CT findings were correlated with the final diagnosis. The efficacies of clinical judgement and CT were evaluated considering simple occlusion as negative and complicated occlusion as positive. According to this, the number of true-positive (TP), false-positive (FP), true-negative (TN) and false-negative (FN) diagnoses was determined. From these values, the sensitivity and specificity of clinical data and CT signs in the detection of complicated occlusion were calculated. Sensitivity was defined as the percentage of patients with complicated obstruction correctly detected ((TP/TP + FN) × 100). Specificity was defined as the percentage of patients with simple obstruction correctly diagnosed ((TN/TN + FP) × 100). Statistical analysis was with Fisher's exact test or Student's *t* test.

Results

Patients

Fifty-four patients were included in the study; there were 30 men and 24 women, ranging in age from 25 to 85 (mean 62) years. The previous laparotomy was for colorectal surgery in 16 cases, appendicectomy in ten, a gynaecological operation in nine, gastric surgery in seven and other procedure in 25, including biliary surgery, aortic replacement, urological operations, intestinal resection and kidney transplantation. Of the 54 patients evaluated, 34 (63 per cent) presented with a complete occlusion at admission.

Diagnosis

Sixteen patients had complicated obstruction confirmed at laparotomy. Three of these patients presented signs of peritoneal irritation at admission (*Table 1*). In these last three cases, the general condition of the patients allowed performance of abdominal CT before the operation. In all 16 patients with a final diagnosis of complicated obstruction, the CT findings suggested the presence of complications at admission (*Table 1*). In this group, 15 patients had CT signs of strangulation, associated with signs of volvulus in eight. Among these 15 patients, the CT diagnosis of strangulation was made on the basis of reduced mural enhancement in seven and was related to the demonstration of at least two of the other signs of severity in the other eight patients. The three patients with peritoneal signs showed mural enhancement on CT. One patient had CT signs of volvulus without associated signs of strangulation (*Table 2*).

Thirty-eight patients had a final diagnosis of simple occlusion; none of them presented peritoneal signs

Table 1 Comparative diagnostic value of clinical and computed tomographic signs for the diagnosis of complicated obstruction

	Complicated obstruction ($n = 16$)	Simple obstruction ($n = 38$)	Sensitivity (%)	Specificity (%)
Clinical diagnosis of complicated obstruction*	3	0	19	100
CT diagnosis of complicated obstruction†	16	3	100	92

*Clinical diagnosis of complicated obstruction was made in the presence of signs of peritoneal irritation; †computed tomographic (CT) diagnosis of complicated obstruction was made in the presence of signs of strangulation (reduced mural enhancement or at least two of the following signs: ascites, mesenteric venous congestion, intramesenteric fluid or mural thickening) or of volvulus (whirl signs and/or radial distribution of the mesentery)

Table 2 Value of computed tomography signs for the diagnosis of complicated obstruction

CT signs at admission	Complicated obstruction ($n = 16$)	Simple obstruction ($n = 38$)	Sensitivity (%)	Specificity (%)
Reduced mural enhancement	7	0	44	100
Ascites	12	7	75	82
Mesenteric congestion	10	5	62	87
Mesenteric fluid	10	0	62	100
Mural thickness	4	5	25	86
Whirl sign and/or radial distribution of the mesentery	9	1	56	97

CT, computed tomography

(*Table 1*). Of the three patients with CT findings that suggested complicated obstruction, one patient had CT signs of volvulus and was operated on as an emergency and two had CT signs of strangulation with the association of ascites and mesenteric venous congestion. Because of the good general condition of these last two patients and their immediate improvement after nasogastric aspiration, the surgeon judged that urgent operation was unnecessary and they received conservative initial treatment before the need for operation became clear. In seven patients with a final diagnosis of simple obstruction, isolated ascites was described on CT at admission.

Clinical outcome

All 16 patients with complicated obstruction were operated on. Intestinal resection for non-viability of the strangulated loop was performed in nine patients, including the three with clinical signs of peritoneal irritation; the remaining seven patients were treated with adhesiolysis only. Four complications were observed in this group including one case of respiratory insufficiency, one urinary infection, one wound infection and one case of septicaemia. One patient with a final diagnosis of simple obstruction was operated on as an emergency on the basis of a CT diagnosis of volvulus, which was not demonstrated at laparotomy. This patient was treated by simple adhesiolysis.

The remaining 37 patients with a simple obstruction were initially treated conservatively. Of these, 28 were relieved without operation, including the two patients with discrete CT signs of strangulation, and nine underwent delayed operation for persisting obstruction after a mean of 60 (range 24–120) h. In the group of nine patients who required delayed operation, intestinal resection for non-separable adhesions was performed in two and adhesiolysis in seven. Four complications were observed in patients with simple obstruction. One patient treated conservatively developed bacteraemia. Among the patients who underwent delayed operation, one with terminal hepatic failure died from multiple organ failure on the first day after a laparotomy performed 24 h after admission, one presented with a wound infection and one who had intestinal resection for non-separable adhesions developed secondary ischaemia of the distal bowel which required a second laparotomy for resection.

There was a significant association between distal location of the obstruction demonstrated on CT performed at admission and the failure of conservative treatment (*Table 3*). In the same patients, plain abdominal radiography performed at admission suggested that the obstruction was proximal in five patients and distal in four. In contrast to the location of the obstruction, the duration of symptoms before admission and the presence of partial or complete obstruction did not significantly affect the outcome after initial conservative management. There was no correlation between previous operative procedure and the evolution after conservative treatment.

Table 3 Evaluation of predictive factors for outcome after conservative initial treatment

	Successful conservative treatment ($n = 28$)	Delayed surgery ($n = 9$)	P
Mean(s.d.) duration of symptoms before admission (h)	49(39)	59(45)	n.s.†
Complete occlusion	16	3	n.s.‡
Distal location*	5	7	<0·01‡

*The location of the occlusion was determined by computed tomography at admission. n.s., Not significant. †Student's t test; ‡Fisher's exact test

Discussion

In cases of ASBO, the early distinction between simple and complicated obstruction, including strangulation and volvulus, is essential to select safely the patients for whom a trial of conservative treatment can be proposed and those who require urgent surgical exploration. Conservative initial treatment may allow a reduction in the number of unnecessary operations in patients with simple obstruction; in contrast, urgent surgery could reduce the morbidity and probably the rate of intestinal resection in patients with complicated obstruction.

As reported previously[1–4], clinical judgement, depending on the presence of signs of peritoneal irritation, was not reliable for early differentiation of simple and complicated obstruction in the present study. In contrast, on the basis of the criteria evaluated, CT was sensitive and specific for the detection of strangulation and volvulus, before the appearance of clinical symptoms.

Reduced mural enhancement was found to be a highly specific CT sign of strangulation but its sensitivity was less than 50 per cent. Similarly, intramesenteric fluid was a very specific but poorly sensitive sign in patients with strangulation; the validity of this particular sign, not previously mentioned, must be evaluated further in larger series. Signs of severity such as ascites or mesenteric congestion were sensitive for the detection of complicated obstruction but their isolated specificity remained limited. Ascites and mesenteric congestion were demonstrated in 12 and ten respectively of the 16 patients with complicated obstruction but also in seven and five of the 38 patients with simple obstruction. Similar observations concerning the presence of ascites in patients with simple obstruction have been described previously with the use of ultrasonography[17]. If the presence of at least two of these severity signs, including ascites, mesenteric congestion, intramesenteric fluid or mural thickening, was required for the diagnosis of strangulation, their combined specificity exceeded 90 per cent.

Independently of the signs of strangulation, volvulus was diagnosed on CT at admission in nearly 20 per cent of the patients evaluated and in nine of the 16 patients with complicated obstruction. The presence of a volvulus was confirmed at laparotomy in all cases but one. Among the patients with a volvulus proven at laparotomy, most had intestinal ischaemia of the twisted loop and four required a resection for non-viability. This observation, in agreement with previous reports[15,18], emphasizes the major pathogenic role of volvulus in ASBO and underlines the need for early surgical treatment of this condition.

Demonstration of the signs of strangulation or volvulus led to CT diagnosis of complicated obstruction with an overall sensitivity of 100 per cent and a specificity superior to 90 per cent. On this basis, CT has a major impact on the early management decision in the authors' experience; in all the patients with complicated obstruction, CT findings prompted urgent laparotomy although this approach was suggested by signs of peritoneal irritation in only three of 16 patients.

When CT signs of severity are isolated or limited, their exact significance has still to be defined. Moreover, CT signs of strangulation indicated by the association of ascites and mesenteric congestion were observed in some patients with a final diagnosis of simple obstruction. Despite initial conservative treatment, none of these patients developed complicated obstruction during follow-up. This could be related either to the non-specificity of these signs or to the reversibility of early ischaemic lesions if they are treated with nasogastric aspiration.

In the management of ASBO, a second question of interest is to differentiate, in patients with a simple obstruction, those who will be relieved with conservative treatment from those who will require operation for persisting obstruction. Accurate location of the obstruction on CT may represent a valuable predictive factor. Patients developing ASBO after appendicectomy or operation on the ovary or tube more frequently require surgical treatment[19]. In these cases, the presence of band adhesions in the pelvis is likely to cause distal obstruction. In the present series, however, the occurrence of persisting obstruction after initial conservative treatment was not related to the type of previous surgery.

In conclusion, these results suggest that CT could play a key role as a first diagnostic procedure in the management of patients with ASBO. In this condition, CT is able accurately to define three categories of patients and specifically direct management in each of these groups: first, patients with strangulation or volvulus that requires urgent surgical treatment; second, patients with a proximal simple obstruction who most probably will be relieved with conservative treatment; and, finally, patients with a simple distal obstruction who will require operation for a persisting occlusion in more than 50 per cent of cases. For these last patients, the ideal treatment has still to be defined; it has been suggested that a semiurgent laparoscopic division of adhesions may be a suitable form of management[19,20].

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Geographical inequality in the provision of carotid endarterectomy in Scotland

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Background Carotid endarterectomy (CEA) is a proven method of stroke prevention in patients with symptomatic and asymptomatic high-grade internal carotid artery stenosis. This study examined whether site of residence affects access to CEA in Scotland.

Methods Scottish Morbidity Record hospital discharge data were collected by the Information and Statistics Division of the National Health Service in Scotland and analysed for the interval 1 January 1989 to 31 December 1995. The number of CEAs performed in the hospitals of each of the 15 regional Health Boards, and CEA rate per 100 000 population resident in each Health Board region, were determined.

Results In 1989, 65 CEAs were performed in the hospitals of five Health Boards and in 1995, 431 CEAs were performed in nine Health Boards. In 1989, the CEA rate per 100 000 resident population varied between 0 (four regions) and 4 (one region), with one region significantly different from Scotland as a whole ($P < 0{\cdot}01$). In 1995, the CEA rate varied between 0 (two regions) and 19 (one region), with two regions significantly different from Scotland as a whole ($P < 0{\cdot}01$).

Conclusion Despite a sixfold increase in the number of CEAs being performed, and a rise in the number of centres performing CEA, there is increasing geographical inequality in the provision of CEA in Scotland.

Two, large multicentre randomized controlled trials have indicated that, in patients with symptomatic internal carotid artery stenosis equal to or exceeding 70 per cent, carotid endarterectomy (CEA) in addition to best medical therapy is associated with a significant reduction in the rate of future stroke compared with best medical therapy alone[1,2]. Although estimates vary widely, the Association of British Neurologists has assessed the incidence of symptomatic carotid artery stenosis to be 43 per 100 000 per year and have suggested that nine patients per 100 000 per year might be candidates for CEA[3]. The Asymptomatic Carotid Atherosclerosis Study (ACAS) has recently shown that CEA, in addition to best medical therapy, does significantly reduce stroke risk in patients with asymptomatic internal carotid artery stenosis equal to or exceeding 60 per cent[4], the incidence of which is estimated to be 800 per 100 000 per year[5]. These data have far reaching implications for the future allocation of resources and personnel to CEA. The aim of this study was to examine whether site of residence in Scotland affects patient access to CEA.

Patients and methods

The National Health Service (NHS) in Scotland comprises 15 regional Health Boards (*Fig. 1*). The Information and Statistics Division (ISD) of the NHS in Scotland collects information on all hospital discharges through the Scottish Morbidity Record 1 (SMR 1). The accuracy of SMR 1 clinical data for main operation is between 85 and 91 per cent, and for main diagnosis approximately 89 per cent[6]. With regard to CEA, the Quality Assessment and Accreditation Unit of the ISD compared SMR 1 data and surgeons' own audit data in 33 hospitals throughout Scotland, and discovered 100 per cent concordance. Between 1 January 1989 and 31 December 1995 (the last year for which complete data are available), the following were obtained for each of the 15 regional Health Boards: the number of individuals resident in each region who were discharged from hospital with a diagnosis of stroke of any aetiology (International Classification of Diseases, ninth revision (ICD-9) codes 430–434, 436, 437); the number of individuals resident in each region who were discharged from hospital with a diagnosis of transient ischaemic attack (TIA) (ICD-9 code 435); the number of individuals resident in each region who died, both in hospital and out of hospital, as a consequence of stroke (all causes); the number of CEAs performed in NHS hospitals in Scotland (Office of Population Census and Surveys (OPCS4) codes L29.4, L29.5); and the number of CEAs performed on the residents of each region. Population estimates from the Registrar General for Scotland were used to calculate the following for each Health Board area: stroke (all causes) incidence and stroke mortality rate per 100 000 resident population; TIA incidence per 100 000 resident population; and the CEA rate per 100 000 resident population.

The Bonferroni method was used to make comparisons between rates in individual Health Boards and Scotland as a whole; a probability value of less than 0·01 was regarded as statistically significant (99 per cent confidence interval, adjusting for the number of tests). The Mann–Whitney U test was used to compare population demographics; $P < 0{\cdot}05$ was regarded as statistically significant (95 per cent confidence interval).

Results

A significantly greater proportion of the population of 14 of the 15 Health Boards was aged 45–64 years in 1995 (median 24 (range 21–25) per cent) compared with 1989

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(median 22 (range 19–24) per cent) ($P<0{\cdot}01$). There was, however, no significant difference in the proportion who were aged 65 years or older (median 16 (range 13–19) per cent) in 1995 *versus* median 15 (range 13–28) per cent in 1989; $P=0{\cdot}65$).

During the 7-year study interval, the annual incidence of hospitalized stroke (all causes), death from stroke and hospitalized TIA varied considerably between Health Boards (*Figs 2–4*) and bore no relationship to the number of CEAs performed (*Fig.* 5). In 1989, the CEA rate per 100 000 resident population ranged between zero in four regions (Highland, Orkney, Shetland and Western Isles) and 4·1 in Tayside, where the rate was significantly higher than in any other region ($P<0{\cdot}01$). In 1995, the CEA rate ranged from zero in two regions (Orkney and Shetland) to 19·0 in Tayside. The operation rates in Ayrshire and Arran (16·7) and Tayside (19·0) were significantly higher than in the other regions ($P<0{\cdot}01$) (*Fig.* 5). The CEA rate in Scotland per 100 000 resident population was 1·3 in 1989 and 8·4 in 1995.

A total of 1731 CEAs were performed between 1989 and 1995. The median age of patients was 63 (range 36–89) years. In 1989, 65 operations were performed in five of 15 Health Board regions whereas in 1995, 431 procedures were performed in nine Health Boards. Seventy-eight per cent of CEAs (1355) were performed in three Health Board areas (Greater Glasgow, Lothian and Tayside). Two centres collaborated in CEA trials. In Lothian, CEA was performed in nine of 17 patients randomized in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) and six of 12 randomized in the Asymptomatic Carotid Surgery Trial (ACST). In Tayside, CEA was performed in 14 of 27 patients randomized in the ACST.

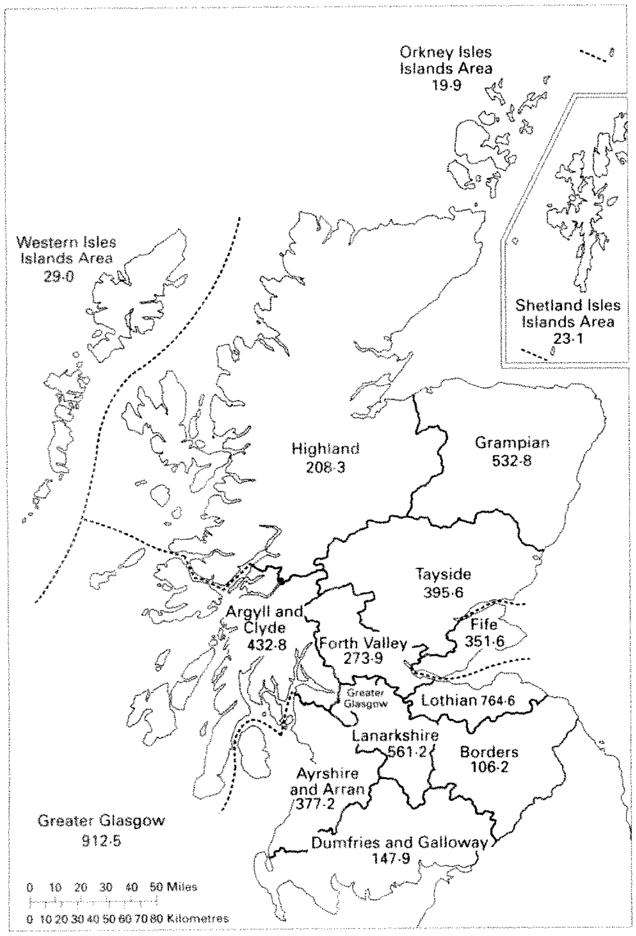

Fig. 1 Population (in thousands at 30 June 1995) and area boundaries (------) of the 15 regional Health Boards in the National Health Service in Scotland

Discussion

There has been a sixfold increase in the number of CEAs performed in Scotland between 1989 and 1995, most of which has occurred since publication of the two large multicentre randomized controlled trials. The CEA rate in Scotland in 1995 was over two and a half times that for the rest of the UK in 1993 (8·5 *versus* 3·3 per 100 000)[7], but less than one-quarter of that in the USA in 1993 (36 per 100 000)[8]. Although it would appear that the CEA rate in Scotland is approaching the level suggested by the Association of British Neurologists[3], there are wide variations in the number of residents in each Health Board region undergoing CEA.

In the present study, no information was available on the indication for surgery, although a guideline produced by the Scottish Vascular Audit Group, of which all Scottish vascular surgeons are members, recommends CEA for symptomatic disease only with stenosis greater than 70 per cent, and for asymptomatic disease only within the context of a clinical trial. Data regarding CEA performed in non-NHS hospitals were not available, but are likely to include a small number of patients.

Despite an overall increase in the number of CEAs performed, and an increase in the number of centres undertaking carotid surgery, there is increasing geographical inequality in the provision of CEA. Such variation in CEA provision has been observed in the USA[9].

Can the differences in CEA provision be explained by differences in stroke and TIA rates between Health Boards? As only a proportion of strokes are due to carotid artery stenosis, and CEA is aimed at preventing and not treating stroke, this question could only be answered definitively by examining Health Board differences in the incidence of carotid territory TIA. Unfortunately, the true incidence of TIA is not known as many patients do not report symptoms, and only a proportion of those who attend their general practitioner are referred to hospital[10].

In the present study, there is no suggestion that the utilization of CEA as a means of stroke prevention is related to the incidence of hospitalized stroke, death from stroke or hospitalized TIA in any particular region, or to differences in patient demography. It is likely that the differences between Health Boards are due to variations in referral practice. Whether it is general practitioners who do not refer a patient to a hospital specialist, or non-surgical specialists who fail to refer patients from regions where a vascular surgeon who performs CEA is not available, remains unknown. The present study clearly indicates that, even in Scotland where the overall CEA rate is the highest in the UK, patients in certain regions may have significantly reduced access to CEA.

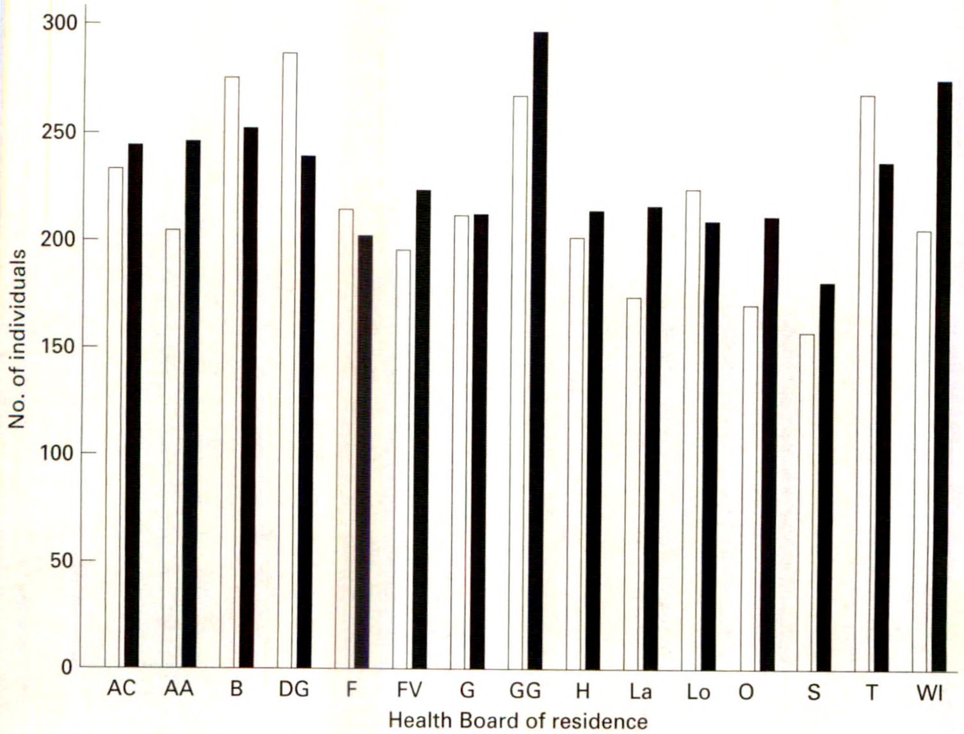

Fig. 2 Annual incidence of hospitalized stroke. Number of individuals discharged from hospital with a diagnosis of stroke (ICD-9 codes 430–434, 436, 437) per 100 000 population by Health Board of residence for 1989 (☐) and 1995 (■). AC, Argyll and Clyde; AA, Ayrshire and Arran; B, Borders; DG, Dumfries and Galloway; F, Fife; FV, Forth Valley; G, Grampian; GG, Greater Glasgow; H, Highland; La, Lanarkshire; Lo, Lothian; O, Orkney; S, Shetland; T, Tayside; WI, Western Isles

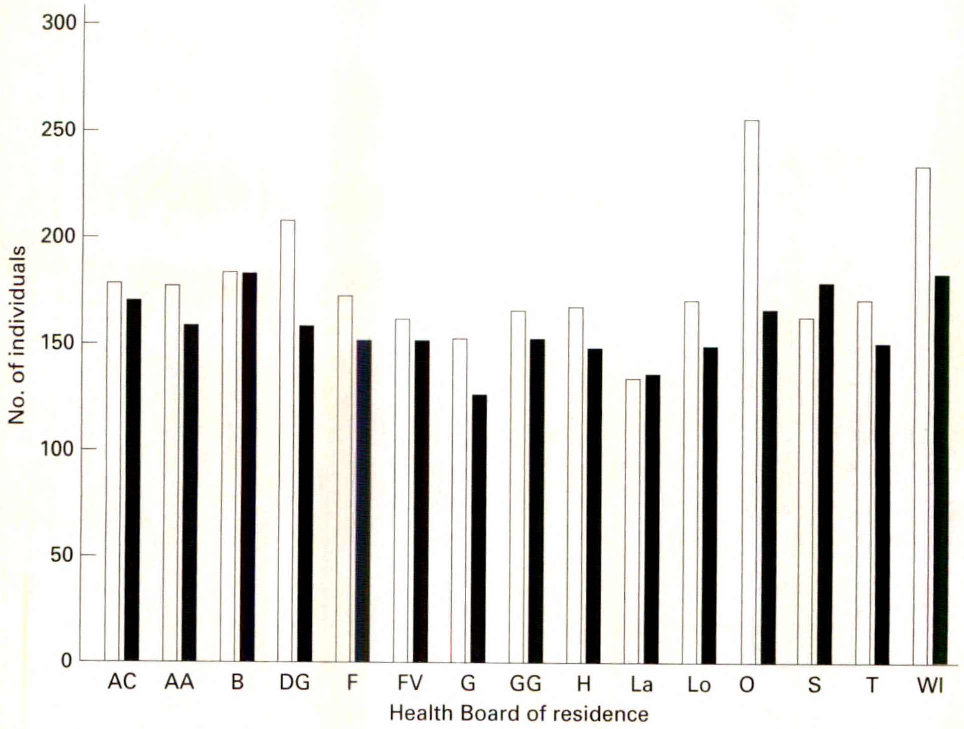

Fig. 3 Annual stroke mortality rate. Number of individuals who died in and out of hospital from stroke per 100 000 population by Health Board of residence for 1989 (☐) and 1995 (■). AC, Argyll and Clyde; AA, Ayrshire and Arran; B, Borders; DG, Dumfries and Galloway; F, Fife; FV, Forth Valley; G, Grampian; GG, Greater Glasgow; H, Highland; La, Lanarkshire; Lo, Lothian; O, Orkney; S, Shetland; T, Tayside; WI, Western Isles

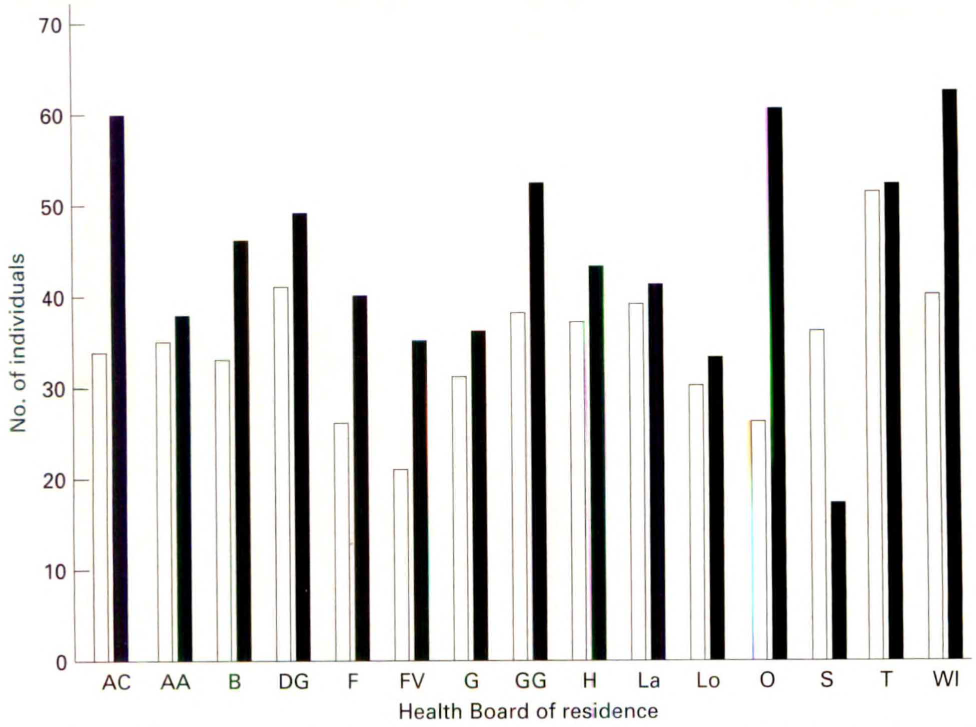

Fig. 4 Annual incidence of hospitalized transient ischaemic attack (TIA). The number of individuals discharged from hospital with a diagnosis of TIA (ICD-9 code 435) per 100 000 population by Health Board of residence for 1989 (□) and 1995 (■). AC, Argyll and Clyde; AA, Ayrshire and Arran; B, Borders; DG, Dumfries and Galloway; F, Fife; FV, Forth Valley; G, Grampian; GG, Greater Glasgow; H, Highland; La, Lanarkshire; Lo, Lothian; O, Orkney; S, Shetland; T, Tayside; WI, Western Isles

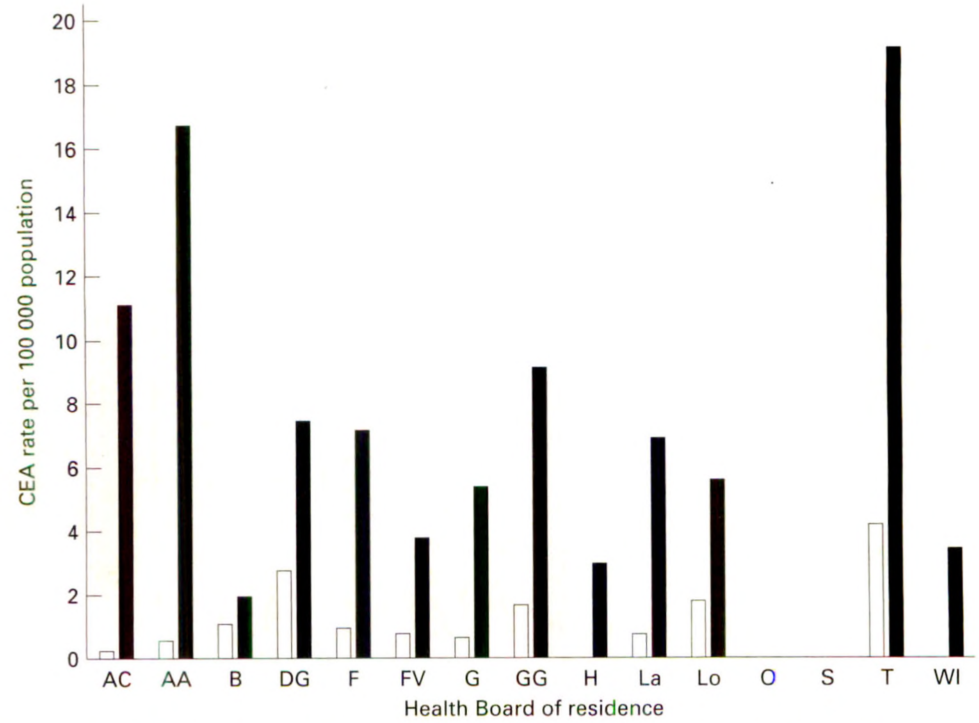

Fig. 5 Carotid endarterectomy (CEA) rate per 100 000 population by Health Board area of residence for 1989 (□) and 1995 (■). AC, Argyll and Clyde; AA, Ayrshire and Arran; B, Borders; DG, Dumfries and Galloway; F, Fife; FV, Forth Valley; G, Grampian; GG, Greater Glasgow; H, Highland; La, Lanarkshire; Lo, Lothian; O, Orkney; S, Shetland; T, Tayside; WI, Western Isles

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Bioflavonoid quercetin scavenges superoxide and increases nitric oxide concentration in ischaemia–reperfusion injury: an experimental study

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Background L-Arginine-depleted environments accompanying ischaemia–reperfusion enhance superoxide production, leading to the formation of reactive oxygen species and a concomitant reduction in basal nitric oxide levels. The bioflavonoid quercetin may prevent these undesirable effects by scavenging superoxide.

Methods Untreated rabbits were compared with those infused with quercetin (5 mg/kg for 2 min) during hindlimb ischaemia (2·5 h) and reperfusion (2 h). In both groups, nitric oxide concentration was measured (porphyrinic microsensor) in the femoral artery wall. Microvasculature changes (morphometry) and superoxide concentration (chemiluminescence) were measured intermittently in biopsies.

Results Approximately 6 min into the period of ischaemia a rapid increase in nitric oxide level from a mean(s.e.m.) basal level of 50(20) to 450(30) nmol/l was observed. In untreated animals, nitric oxide concentration dropped to an undetectable level (less than 1 nmol/l) during reperfusion. In quercetin-treated animals, the decrease in nitric oxide concentration was slower, such that substantial amounts (60(20) nmol/l) accumulated during reperfusion. In biopsies after ischaemia–reperfusion maximal calcium ionophore A23187-stimulated nitric oxide concentration increased (25-30 per cent) in the presence of quercetin, while the superoxide concentration decreased.

Conclusion Quercetin treatment mollified ischaemia–reperfusion injury to skeletal muscle by scavenging destructive superoxide and enhancing the cytoprotective nitric oxide concentration.

Increased production of reactive oxygen species during ischaemia–reperfusion injury leads to a consumption and depletion of endogenous scavenging antioxidants[1]. The consequences of such injury, frequently observed in surgical patients, are local and remote tissue destruction, and sometimes the death of the patient[2,3].

Acting on encouraging epidemiological studies[4] suggesting a possible protective role of moderate alcohol intake (in particular red wine) on the incidence of coronary heart disease ('the French paradox'), Fitzpatrick *et al.*[5] recently investigated the effects of various components of grapes on rat aortic rings. Among the major components of red grape skin, they found that quercetin (a low molecular weight bioflavonoid) relaxed rat aortic rings (precontracted with phenylephrine) while it significantly increased the intracellular concentration of guanosine 3′, 5′-cyclic monophosphate, the product of nitric oxide-agonized enzyme. These quercetin-induced effects were obliterated by denuding the constitutive nitric oxide synthase (cNOS)-studded endothelium, or by incubation with inhibitors of cNOS. Therefore, it was suspected that quercetin might interact with endothelial cNOS, or its products.

Under normal conditions in mammalian tissue, cNOS receives and stores enough electrons from reduced nicotinamide adenine dinucleotide phosphate (NADPH) to transform its substrates oxygen and L-arginine into its products L-citrulline, nitric oxide and water[6]. Under abnormal conditions, in L-arginine or (6R)-5,6,7,8-tetrahydrobiopterin (H_4B)-depleted environments, it has been demonstrated *in vitro* that at least one cNOS isoform can still receive electrons from NADPH and, when activated, donate them to its substrate oxygen alone, resulting in the formation of superoxide[7]. Living mammals, freshly excised tissue, or even tissue cultures naturally contain a large concentration of superoxide dismutase (SOD; 5–10 μmol/l) that rapidly converts superoxide into hydrogen peroxide[8], and a similarly large concentration of catalase that converts hydrogen peroxide into water and oxygen at a more moderate rate[8]. Nitric oxide and hydrogen peroxide are potent vasodilators[9,10], and superoxide is a potent vasoconstrictor[11]. However, the product of the rapid ($k = 6{\cdot}7 \times 10^9$ litres per mol per s)[12] reaction of nitric oxide with superoxide, peroxynitrite, is a relatively impotent vasodilator[13].

Since the amount of SOD in tissue cannot effectively prevent the non-enzymatic reaction of nitric oxide with superoxide as long as basal concentrations of nitric oxide are maintained, at least two major strategies may possibly prevent excess superoxide production and subsequent ischaemia–reperfusion injury. The first is based on treatment with H_4B, L-arginine or their analogues, thus preventing L-arginine- and H_4B-deficient conditions so cNOS will not produce excessive superoxide[14]. The second is based on scavenging superoxide already produced by cNOS and other potential sources of superoxide by using SOD and other free radical scavengers[15]. This paper describes the use of the second strategy, and tested the hypothesis that pretreatment with quercetin would mollify

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ischaemia–reperfusion injury by affecting the superoxide and nitric oxide production. In these experiments continuous *in vivo* measurement of nitric oxide production was correlated with intermittent measurement of superoxide production. Microvasculature changes (microvessel cross-sectional area alterations) were measured morphometrically as an indicator of ischaemia–reperfusion injury.

Materials and methods

Animal preparation for in vivo *studies*

The *in vivo* studies were performed on adult male New Zealand white rabbits (Charles River, Sulzfeld, Germany) according to the 'Guiding Principles in the Care and Use of Animals'. The rabbits had free access to food (Altromin 2120 standard diet pellets; Marek, Vienna, Austria) and water.

Rabbits anaesthetized using a mixture of ketamine hydrochloride 15 mg/kg and xylazine hydrochloride 1·5 mg/kg were intubated and ventilated with nitrous oxide–oxygen and isoflurane (concentration 1–2 vol per cent). Ventilator parameters were adjusted according to blood gas values to achieve the normal range of partial pressures of oxygen and carbon dioxide, and pH and oxygen saturation in arterial blood samples obtained from the carotid artery. Blood arterial pressure was monitored in the carotid artery (physiological pressure transducer; Berg, Kirchseeon/Eglharting, Germany). Blood flow was measured with the Transonic System (Model T 106, Ithaca, USA).

Bilateral hindlimb ischaemia was achieved according to an established technique[16]. Blood flow occlusion as well as reperfusion were confirmed with a blood perfusion monitor (Laserflo BPM2; Vasamedics, St Paul, Minnesota, USA). The hindlimb ischaemia time was 2·5 h followed by 2 h of reperfusion. Animals ($n = 7$) were treated by intravenous infusion into the auricular vein of a water-soluble form of quercetin (5 mg/kg over 2 min). Ischaemia was started 40 min after quercetin infusion. The animals subjected to ischaemia–reperfusion but without quercetin treatment received a placebo infusion of 0·9 per cent saline and served as controls ($n = 7$).

Preparation of nitric oxide sensors for in vitro *and* in vivo *measurements*

Preparation of the catheter-protected porphyrinic sensor[17–19] was slightly different from that previously described[20]. Specifically, the needle shaft was truncated 3 mm shorter, instead of 0·5 mm longer, than its protective catheter. Using a 24-G placement needle (clad with its catheter with two 50-μm ventilation holes near the tip), femoral artery smooth muscle tissue was pierced, then the needle was advanced to the desired place in the vessel wall. The position of the catheter was secured, and the placement needle was removed and replaced by a 24-G porphyrinic nitric oxide sensor.

For positioning the flexible active tip of the porphyrinic sensor on a microvessel, a lower limb of a rabbit was positioned under a dissecting microscope. Surgical microdissection was performed until a microvessel (mean(s.e.m.) (50) μm) was visualized. Then, a porphyrinic sensor was lowered with the help of a stereotactic micromanipulator until the surface of the observed blood vessel was reached. A platinum wire counterelectrode and a reference silver/silver chloride electrode were placed in contact with adjacent tissue.

Differential pulse voltammetry (DPV) or chronoamperometry was performed using a PAR model 273 voltammetric analyser (potentiostat plus waveform generator; EGG Princeton Applied Research, Oak Ridge, USA) interfaced with an IBM 80 486 computer (Gateway, North Sioux City, USA) with data acquisition and control software. DPV was used to measure the basal nitric oxide concentration. Chronoamperometry was used for fast (resolution time 0·1–1 ms) and continuous measurement of the changes in nitric oxide concentration from basal level with time. Linear calibration curves were constructed for each sensor from 2×10^{-9} to 2×10^{-5} mol per litre nitric oxide, before and after measurements, with aliquots of saturated nitric oxide prepared as described previously[21].

Indirect and direct superoxide measurement

To determine the superoxide concentration in freshly excised tissue indirectly nitric oxide release was stimulated with a calcium ionophore (A23187, 10 μmol/l), and the nitric oxide concentration was measured in the presence and absence of SOD 100 units ml as described above. The difference in concentrations was assumed to be equal to the superoxide concentration.

To confirm the indirect method, the superoxide concentration was determined directly by a chemiluminescence method in fresh biopsies[22]. Superoxide produced chemiluminescence of lucigenin (bis-*N*-methylacridinium nitrate; Aldrich Chemical Company, Milwaukee, Wisconsin, USA), which was detected with a scintillation counter (Beckman 6000LS, with a single photon monitor; Beckman, Fullerton, USA). Each tissue sample (8–15 mg) was placed in 2 ml Hanks' Balanced Salt Solution (HBSS; Sigma Chemical Company, St Louis, Missouri, USA) adjusted to pH 7·4 at 25°C, then enough lucigenin was added to give a concentration of 0·25 mmol/l. Basal superoxide concentration produced by the tissue was measured after a 2-min incubation in HBSS. The sum of the superoxide produced by the L-arginine- or H_4B-depleted cNOS and other sources (stimulated) was measured in a similar manner, except the 2-min incubation period was followed by injection of 20 μl of A23187 1 mmol/l (a receptor-independent cNOS agonist). Photon counts were calibrated by constructing standard curves of superoxide concentration generated stoichiometrically by treating xanthine with xanthine oxidase.

Morphological investigations

Adductor magnus muscle tissue samples were removed from the hindlimb before the onset of ischaemia, at the end of ischaemia and 2 h after reperfusion. Tissue samples were immediately immersed for quick freezing at −70°C in a 2-methylbutane solution (Uvasol; Merck, Darmstadt, Germany) for 2 min. The samples were stored at −80°C until they were sectioned. Transverse cryosections of 10 μm thickness (Kryostat 1720; Leitz, Germany) were stained for actomyosin adenosine 5′-triphosphatase (ATPase) activity at pH 4·3 and were examined by light microscopy (Axiomat; Zeiss, Oberkochen, Germany). Capillaries were measured with a pen linked to a personal computer using a semiautomatic image-analysing system (LUCIA M; Nikon Laboratory Imaging, Prague, Czech Republic) at a 1000-fold magnification. Fifty microvessels per random field were measured in each section, and the microvessel cross-sectional area was determined. After completion of the experimental investigation, the animals were killed by intravenous administration of an overdose of potassium chloride.

Statistical analysis

Data are expressed as mean(s.e.m.). Statistical analysis was by unpaired Student's *t* test or by analysis of variance followed by Schette's test. Means were considered statistically different at $P < 0·05$.

Results

A typical chronoamperometry curve (current calibrated as nitric oxide concentration *versus* time) was obtained from *in situ* measurement of nitric oxide in a freshly excised rabbit aorta (*Fig. 1a*). Immediately after administration of a receptor-independent cNOS stimulator, A23187 10 μmol/l, an initial rapid increase in nitric oxide concentration was observed. The peak concentration of nitric oxide was 310(30) nmol/l. This peak concentration increased to 420(35) nmol/l after A23187 stimulation of nitric oxide in the presence of quercetin 4 µmol/l. A similar increase in nitric oxide concentration was observed in the presence of SOD 100 units/ml (*Fig. 1b*); nitric oxide peak concentration increased from 300(30) to 405(20) nmol/l.

It was hypothesized that quercetin is a rapid scavenger of superoxide like SOD and either compound was used in the indirect estimation of superoxide production at the time of nitric oxide release. Nitric oxide concentration enhancement (by rapid superoxide scavenging by quercetin) increased as the concentration of quercetin increased up to 30 µmol/l (*Fig. 2*). At quercetin concentrations higher than 30 µmol/l a rapid decline in the beneficial effect on production of nitric oxide was observed. That quercetin was scavenging superoxide was substantiated by the use of a chemiluminescence method to make direct *in vitro* measurements of superoxide concentration in freshly excised aorta. The basal concentration of superoxide in the tissue (before A23187 stimulation of cNOS) was 12(3) nmol per litre per mg tissue ($n = 7$); it decreased to 6(1) nmol per litre per mg tissue in the presence of quercetin (*Fig. 3*). After A23187 stimulation, superoxide concentration increased to 27(3) nmol per litre per mg tissue in the absence of quercetin. However, in the presence of quercetin 10 µmol/l the superoxide concentration decreased to 7(1) nmol per litre per mg. This is significantly lower than in the absence of quercetin ($n = 7$, $P < 0{\cdot}005$) (*Fig. 3*).

A typical chronoamperometry curve was obtained from the *in vivo* measurement of nitric oxide concentration with the sensor placed in the wall of the femoral artery. Administration of quercetin (5 mg/kg over 2 min), without subsequent femoral artery clamping, caused an increase in nitric oxide concentration to 110(20) nmol/l ($n = 7$) above its basal level (*Fig. 4*). The increase in nitric oxide concentration was accompanied by a decrease in blood pressure of 20 mmHg (*Fig. 4*).

A nitric oxide sensor placed in the wall of the femoral artery *in vivo* showed an increase in nitric oxide production shortly (340(30) s) after the femoral artery was clamped (*Fig. 5a*). The concentration of nitric oxide reached a peak (450(30) nmol/l) and after that dramatically decreased with time (40 min) below its original basal concentration (50(20) nmol/l). Treatment with quercetin was quickly followed by an increase in nitric oxide concentration with a simultaneous decrease in blood pressure (*Fig. 5b*). After the femoral artery was clamped an initial burst of nitric oxide production (maximum 440(30) nmol/l) was observed, which later decreased gradually approximately to its basal level. During reper-

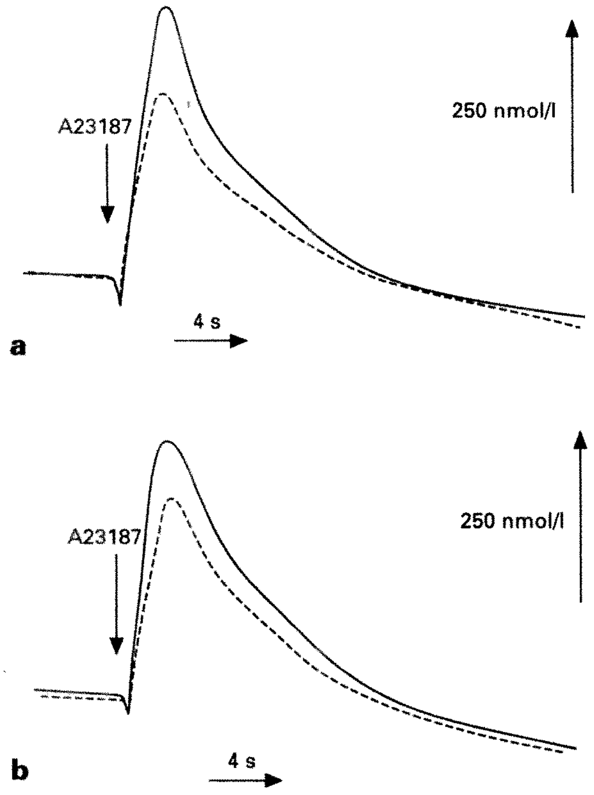

Fig. 1 *In vitro* measurement of nitric oxide concentration from rabbit aorta a in the absence (– – – –) and presence (———) of quercetin 4 µmol/l and b in the absence (– – – –) and presence (———) of superoxide dismutase 100 units/ml. A calcium ionophore (A23187, 10 µmol/l) was used to stimulate nitric oxide release

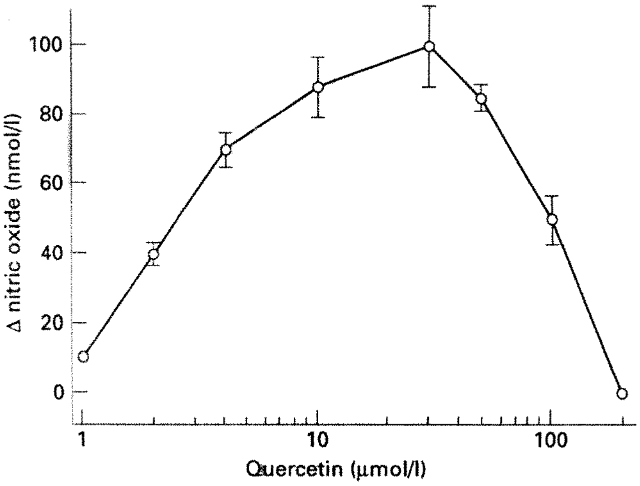

Fig. 2 Mean(s.e.m.) difference in nitric oxide concentrations measured in the presence and absence of quercetin (Δ nitric oxide), as a function of quercetin concentration

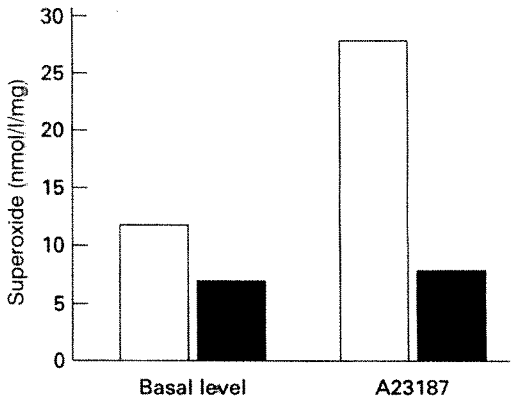

Fig. 3 Concentration of superoxide in aorta in the absence (□) and presence (■) of quercetin 10 µmol/l. Superoxide concentration was measured before (basal level) and after (total level) stimulation with a calcium ionophore (A23187, 10 µmol/l)

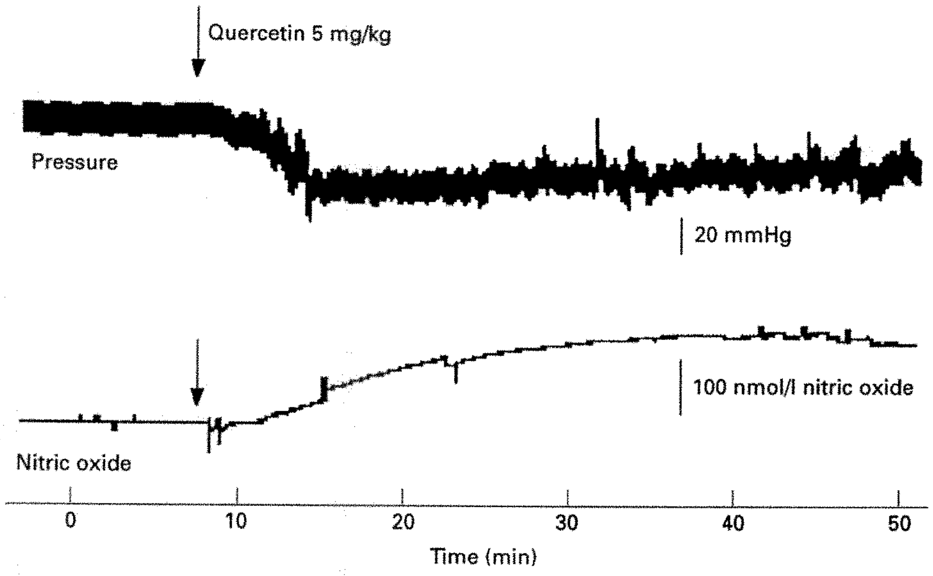

Fig. 4 *In vivo* measurement of nitric oxide concentration in the wall of the femoral artery during intravenous infusion of quercetin (5 mg/kg over 2 min). Changes in arterial blood pressure are also shown

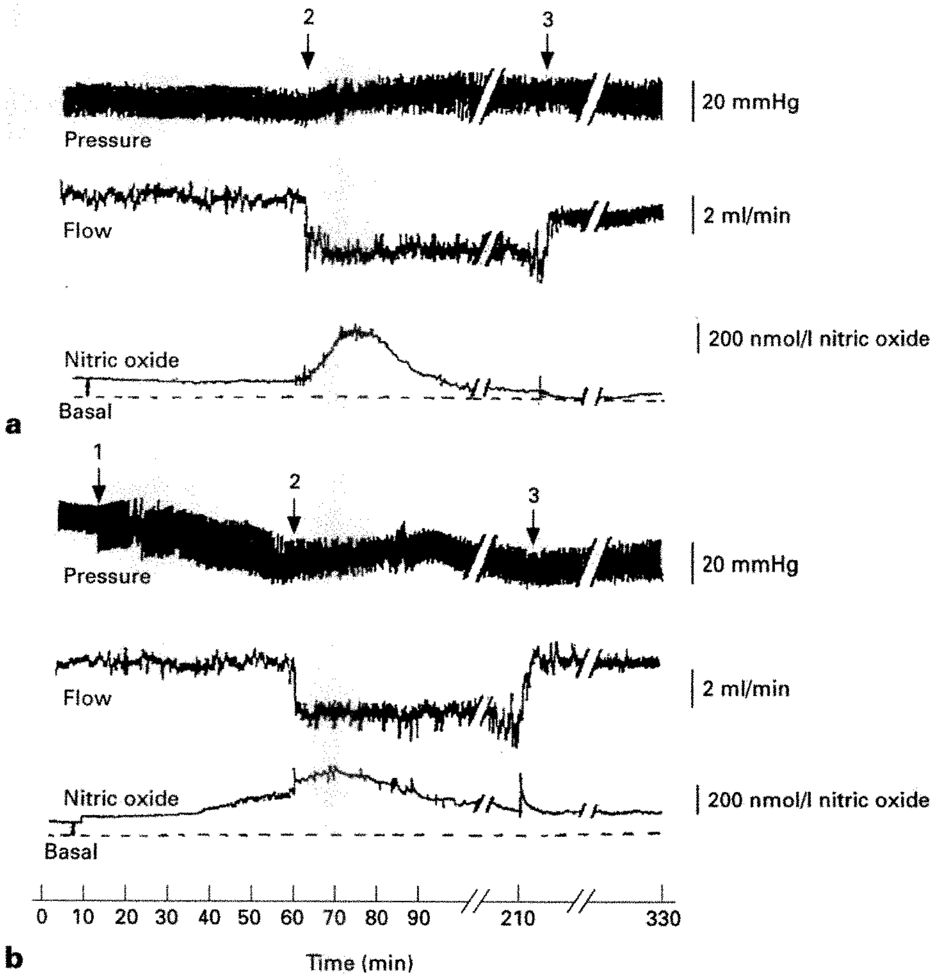

Fig. 5 *In vivo* measurement of nitric oxide release in the wall of the femoral artery during ischaemia and reperfusion (rabbit limb) **a** without quercetin and **b** with quercetin (5 mg/kg over 2 min). Time course marks 1, infusion of quercetin; 2, beginning of ischaemia; 3, beginning of reperfusion

fusion, the nitric oxide concentration remained constant, and flow increased above its preischaemic level without a change in pressure.

Morphological changes

No significant changes in the size of microvessels in skeletal muscles of untreated animals were observed during the ischaemia period. However, 2 h after reperfusion, significant microvessel constriction was documented: the microvessel cross-sectional area decreased from $19{\cdot}15(0{\cdot}76)\,\mu m^2$ at the end of ischaemia to $12{\cdot}64(1{\cdot}15)\,\mu m^2$ after 2 h of reperfusion ($P < 0{\cdot}005$). In the muscles of quercetin-treated animals, no significant change in microvessel size was observed either at the end of ischaemia or 2 h after reperfusion.

Discussion

The model underlying these studies is that in the L-arginine-deficient environment accompanying ischaemia cNOS may initiate high production of superoxide and lead to rapid scavenging of nitric oxide to form peroxynitrite[14]. Although peroxynitrite is relatively stable, when protonated ($pK_a = 6{\cdot}8$), the rapidly formed peroxynitrous acid ($t_{1/2}$ less than 1 s) rearranges to form the relatively harmless hydrogen cation and nitrate anion[23]. However, any process that increases the local nitric oxide or superoxide concentration may cause the local peroxynitrous acid concentration to become sufficient enough to assure its efficient transport to reactive sites as far as several cell diameters away[23]. In the vicinity of certain reactive centres, peroxynitrous acid may undergo homolytic cleavage to hydroxyl free radical and nitrogen dioxide free radical, or heterolytic cleavage to nitronium cation and hydroxide anion[14]. Three of these cleavage products (hydroxyl free radical, nitrogen dioxide free radical and nitronium cation) are among the most reactive and damaging species in biological systems, and may initiate a cascade of events leading to severe ischaemia–reperfusion damage[23].

As evident from the data obtained, quercetin may increase total nitric oxide concentration by scavenging superoxide. At the maximum effective concentration of $30\,\mu$mol/l, quercetin appears to be a more potent scavenger of superoxide than SOD 100 units/ml (approximately the normal physiological concentration of SOD)[8]. The apparently larger amount of superoxide scavenged by quercetin displayed in *Fig. 1a* is most likely the result of prolonged nitric oxide production by endothelial cNOS. Quercetin certainly scavenges superoxide[24], but it is also known as a protein kinase C inhibitor[25]. Endothelial cNOS is normally turned off by phosphorylation of one of its serine residues by a phosphate group provided by protein kinase C a minute or so after the endothelial cNOS is turned on[26]. It is suggested that quercetin is not only a good scavenger of superoxide but that it also prolongs the endothelial cNOS burst by inhibiting protein kinase C, the enzyme that provides the negative switch.

Furthermore, high concentrations of quercetin have been reported to inhibit the nitric oxide generating activity of endothelial cNOS ($IC_{50} = 220\,\mu$mol/l)[27]. It is evident from *Fig. 3* that quercetin also effectively inhibits the superoxide generating activity ($IC_{50} = 100\,\mu$mol/l). However, the exact cause(s) may be difficult to ascertain, since plant phenols display a multiplicity of other biochemical actions, such as inhibition of the sacroplasmic reticulum calcium ATPase in skeletal muscle, stimulation of cardiac sacroplasmic recticulum calcium ATPase, and inhibition of the sodium–potassium ATPase and phosphodiesterase, which complicate interpretation of the effects at the cell or tissue level[27].

B-dihydroxy flavones like quercetin produce hydrogen peroxide after scavenging superoxide[28]. *In vivo*, this is usually not a problem because there is sufficient catalase present to rapidly convert the hydrogen peroxide into water and oxygen[8]. However, the ubiquitous presence of free ferrous ion accompanying *in vitro* studies will rapidly convert hydrogen peroxide into hydroxyl free radical (Fenton reaction), the most destructive species in biological systems[28]. At least one *in vitro* study[28] reports that quercetin accelerates the production of hydroxyl free radicals in the presence of ferrous ion (most probably quercetin rapidly transforms the existing superoxide into hydrogen peroxide, then the Fenton reaction works rapidly). *In vivo* systems are protected from this disastrous reaction by the iron transporter, ferritin, which quickly scavenges any free ferrous ion.

In general, direct, but intermittent, chemiluminescent measurements of superoxide in freshly excised tissue during the course of ischaemia–reperfusion provide strong indications that superoxide can be produced in relatively high concentrations during ischaemia–reperfusion. Furthermore, this superoxide production is inversely related to nitric oxide accumulation continuously measured by the nitric oxide sensor. A dramatic decrease in nitric oxide concentration was observed during reperfusion when production of superoxide was the highest. Paralleling this low nitric oxide concentration during reperfusion, a significant decrease in the diameter of microvessels was observed[14].

Treatment with quercetin before ischaemia–reperfusion prevented significant accumulation of superoxide and helped to maintain the concentration of nitric oxide at its basal level during reperfusion. The physiological level of nitric oxide prevented microvessel constriction in reperfused muscle.

In conclusion, the present study demonstrates that quercetin may be useful in protecting skeletal muscle from ischaemia–reperfusion injury. Nitric oxide deficiency due to its consumption by superoxide produced at a high concentration during ischaemia–reperfusion plays an important role in the pathophysiology of ischaemia–reperfusion injury. Quercetin treatment prevents excessive accumulation of superoxide and preserves nitric oxide concentration at a level sufficient to maintain vasorelaxation in the surrounding smooth muscles, while inhibiting platelet aggregation and adhesion within the lumen.

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Influence of ischaemia–reperfusion injury on CD44 expression in rat small intestine

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Background CD44 is an adhesion molecule expressed by neutrophils and lymphocytes which is involved in cell–cell and cell–matrix binding. In this study, the effect of ischaemia–reperfusion injury on CD44 messenger RNA (mRNA) and cell surface immunohistochemical expression of CD44 in the rat small intestine was evaluated.

Methods Wistar rats ($n = 16$) were randomized to either serve as controls (sham surgery) or to be subjected to a standardized ischaemia–reperfusion injury (suprarenal aorta occluded for 1 h followed by 1 h of reperfusion). Standardized segments of jejunum were harvested after ischaemia–reperfusion injury (ischaemic and reperfused samples) to measure the mucosal protein and DNA content, mRNA expression of CD44 and the immunohistochemical expression of CD44.

Results Reperfusion significantly damaged the jejunal mucosa, e.g. mucosal protein content was lower after reperfusion compared with that in the control group ($z = -2{\cdot}31$, $P = 0{\cdot}02$) and the ischaemic samples ($z = -2{\cdot}52$, $P = 0{\cdot}01$). The expression of cell surface CD44 protein was also significantly decreased after ischaemic injury ($z = -1{\cdot}99$, $P = 0{\cdot}04$); this coincided with a decrease in the amount of cytoplasmic CD44 mRNA within isolated enterocytes ($z = -2{\cdot}31$, $P = 0{\cdot}02$).

Conclusion Ischaemia–reperfusion injury decreases the expression of CD44 within the jejunal mucosa. This may contribute to the failure of the gut barrier after such injury.

The migration, accumulation and activation of polymorphonuclear neutrophils (PMNs) is a key event in ischaemia–reperfusion injury[1,2]. CD44 is a transmembrane glycoprotein expressed by neutrophils and lymphocytes which is involved in cell–cell and cell–matrix binding. Hence CD44 may play a key role in events such as PMN migration, lymphocyte homing and cancer metastasis[3–6]. In this study, the effect of ischaemia–reperfusion injury on CD44 messenger RNA (mRNA) and immunohistochemical expression of CD44 in the rat small intestine was evaluated.

Patients and methods

Sixteen male Wistar rats (300–350 g) were allowed 1 week to acclimatize before surgery. The rats were exposed to a daily 12-h light–dark cycle, and fed water and rat chow (Milne Stockfeeders, Perth, Australia) *ad libitum*. This study was approved by the Royal Perth Hospital Animal Ethics Committee.

Surgical procedures

The rats were anaesthetized by an intraperitoneal injection of pentobarbitone sodium 50 mg per kg body-weight. They were then placed on a heating pad and a midline incision was made in the abdomen. The animals were randomized to either serve as controls (sham surgery) or to be subjected to a standardized ischaemia–reperfusion injury (suprarenal aorta occluded for 1 h followed by 1 h of reperfusion). Standardized circumferential and full-thickness biopsies were taken from the proximal jejunum of animals in the control group. The suprarenal aortas of the remaining animals were occluded with a vascular clamp before closure of the abdomen. After 1 h, the abdomens were reopened and standardized circumferential and full-thickness biopsies were taken from the proximal jejunum (ischaemic samples). The vascular clamps were then removed from the aorta and the abdomens were closed. After 1 h of reperfusion, the abdomens were reopened and further standardized circumferential and full-thickness biopsies were taken from the proximal jejunum (reperfused samples).

Harvesting of tissues

The ischaemic samples were divided into portions 0·5 and 3·0 cm long. The 0·5-cm segments were slit down the mesenteric border, embedded in Optimal Cutting Temperature (OCT) Compound (Sakura Finetechnical, Tokyo, Japan) and immediately snap-frozen in liquid nitrogen for immunohistochemistry. The 3·0-cm segments were weighed, slit down the mesenteric border and the mucosa was stripped away from the submucosa using a glass slide (depth confirmed by histology). The samples of mucosa were weighed, placed in 5 ml of homogenizing buffer (potassium hydrogen phosphate 125 mmol/l, sucrose 330 mmol/l, dithiothreitol 2 mmol/l, pH 7·6) and homogenized (Ultra Turrax; Janke and Kunkel, Staufen, Germany).

The reperfused samples and control samples were divided into portions 0·5, 3·0 and 10·0 cm long. The 0·5- and 3·0-cm segments were treated in the manner described for the ischaemic samples. Enterocytes were isolated from the 10·0-cm segments using the method described by Weiser[7]. Briefly, the segments of bowel were flushed with normal saline, filled with disrupting solution (potassium chloride 1·5 mmol/l, sodium chloride 96 mmol/l, sodium citrate 27 mmol/l, potassium dihydrogen phosphate 8 mmol/l, disodium hydrogen phosphate 5·6 mmol/l, pH 7·3) and incubated for 15 min at 37°C. The disrupting solution was replaced with collection buffer (sodium chloride 13·6 mmol/l, potassium chloride 0·26 mmol/l, potassium dihydrogen phosphate 0·14 mmol/l, disodium hydrogen phosphate 0·81 mmol/l, ethylenediamine tetra-acetic acid 1·5 mmol/l, dithiothreitol 0·5 mmol/l, pH 7·4) and the segments of bowel were incubated for a further 15 min. The segments were patted with the finger tips, the isolated enterocytes were collected into a centrifuge tube and the tubes were centrifuged at 500*g* for 5 min at 4°C. The isolated enterocytes were immediately snap-frozen in liquid nitrogen and stored at −70°C.

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Immunohistochemistry

The samples frozen in optimal cutting temperature compound were sectioned on to glass slides at 6 μm using an Ames Cryostat II (Miles). Immunohistochemical staining was performed using an indirect immunoperoxidase technique[8]. The primary antibody was a mouse antirat CD44 antibody (MRC OX-50; Serotec, Oxford, UK) diluted 1 : 100. The secondary antibody consisted of biotinylated sheep antimouse immunoglobulins (Amersham Australia, Sydney, Australia) containing 10 per cent normal rat serum. The tertiary antibody was a streptavidin–horseradish peroxidase conjugate (Amersham Australia). Sections were counterstained with haematoxylin and peroxidase-positive cells were identified morphometrically by brown staining around the cytoplasm. Positive cells were expressed as the number of positive cells per 1000 enterocytes. At least ten villi or 1000 enterocytes were counted per section.

Biochemistry

Aliquots of the mucosal homogenates were taken to estimate protein content by the method of Lowry *et al.*[9] using bovine serum albumin as the standard and DNA content by the method of Larbarca and Paigen[10] using calf thymus DNA as the standard.

Molecular biology

RNA was separated from the isolated enterocytes using RNAzol B (Bresatec, Adelaide, Australia). RNA integrity was confirmed by electrophoresis on a 1 per cent denaturing agarose gel. The RNA content was measured by ultraviolet spectrophotometry and samples were then diluted to 1 μg/μl with diethyl pyrocarbonate-treated water. The RNA was reverse transcribed using avian myeloblastosis virus reverse transcriptase (Promega, Sydney, Australia) and 5 μl of the resultant complementary DNA was subjected to polymerase chain reaction (PCR). The PCR reaction mix contained deoxyribonucleoside 5′-triphosphates 200 μmol/l, 1 × PCR buffer (Boehringer Mannheim, Sydney, Australia), 0·5 units Taq DNA polymerase (Boehringer Mannheim) and 0·16 μmmol/l each of the forward and reverse primers. The forward primer sequence for CD44 was 5′GGTGCATTTGGTGAACAAGG3′ and the reverse primer sequence was 5′AAAGGACCTCCAGGGTTTGA3′, resulting in a product of 676 base pairs[11]. β-actin mRNA was used as an internal control. The forward primer sequence for β-actin was 5′ATGGATGACGATATCGCTG3′ and the reverse primer sequence was 5′ATGAGGTAGTCTGTCAGGT3′, resulting in a product of 568 base pairs[12].

The PCR was carried out for 45 s at 94°C, 45 s at 55°C and 90 s at 72°C for 35 cycles. Preliminary work indicated that the amplification was in the exponential phase at 35 cycles. Aliquots of the PCR reaction mixes (5 μl) were electrophoresed on 6 per cent polyacrylamide gels, stained with SYBR Green I (1 : 10 000; Molecular Probes, Eugene, USA) and scanned using the FluorImager SI computer package (Molecular Dynamics, Melbourne, Australia). The intensity of the product bands was measured using Image Quant software (Molecular Dynamics) and expressed as a ratio of CD44 to β-actin products.

Statistical analysis

Results are expressed as mean(s.d.). Comparisons were made using the Mann–Whitney *U* test for independent samples and the Wilcoxon matched pairs signed rank test for related samples. A probability of a type I error of less than 5 per cent was considered to be statistically significant.

Table 1 Effect of ischaemia–reperfusion on the jejunal mucosa

	Control ($n = 8$)	Ischaemia–reperfusion injury ($n = 8$)	
		Ischaemic	Reperfused
Protein content (μg/mg)	38·14(7·54)	36·53(9·19)	24·47(10·27)
DNA content (μg/mg)	7·54(2·18)	6·49(2·45)	3·47(1·98)

Values are mean(s.d.)

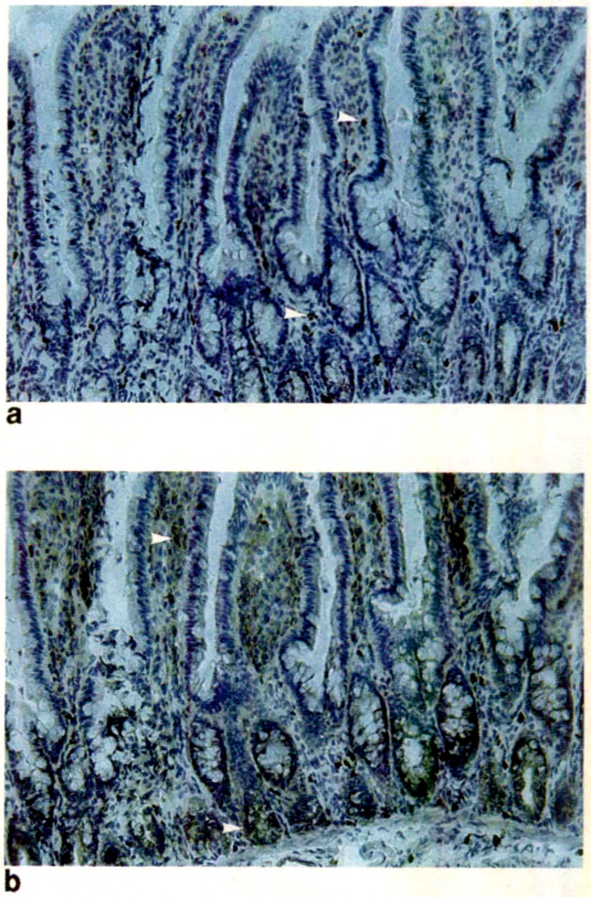

Fig. 1 Effect of ischaemia–reperfusion on CD44 expression in the jejunum. **a** Negative control; note the granular endogenous peroxidase (arrows). **b** CD44 expression around the villous tips and crypts; positive cells were identified by brown staining (arrows) around the cytoplasm (haematoxylin counterstain; original magnification × 40)

Results

Reperfusion significantly damaged the jejunal mucosa (*Table 1*). Mucosal protein content was lower after reperfusion compared with that in both the control group ($z = -2\cdot31$, $P = 0\cdot02$) and the ischaemic samples ($z = -2\cdot52$, $P = 0\cdot01$). In addition, the reperfused samples had a lower mucosal DNA content than the control samples ($z = -2\cdot62$, $P = 0\cdot01$) and the ischaemic samples ($z = -2\cdot38$, $P = 0\cdot02$). Histological examination confirmed that 1 h of ischaemia followed by 1 h of reperfusion produced ischaemia–reperfusion injury. The degree of intestinal tissue damage ranged from the development of subepithelial space at the villous tip, to epithelial lifting along the villous sides, i.e. grade I–III lesions[13,14].

The expression of cell surface CD44 protein was decreased after ischaemia–reperfusion injury. In the control group 119·9(39·3) cells per 1000 enterocytes expressed surface CD44, while 73·5 (40·0) cells were stained in the ischaemic samples ($z = -1\cdot99$, $P = 0\cdot04$). Reperfusion tended to decrease CD44 surface expression (76·4(30·6) positive cells). However, this was not significant compared with either the control group ($z = -1\cdot78$, $P = 0\cdot07$) or the ischaemic samples ($z = -0\cdot14$, $P = 0\cdot89$). This coincided with a significant decrease in the ratio of cytoplasmic CD44 to β-actin mRNA within isolated enterocytes: 1·00(0·14) in the control group *versus* 0·73(0·25) in reperfused samples ($z = -2\cdot31$, $P = 0\cdot02$). CD44 was expressed in the crypts and villous tips of the jejunum in rats after ischaemia–reperfusion injury (*Fig. 1*).

Discussion

It was found that 1 h of ischaemia followed by 1 h of reperfusion produced morphological and biochemical changes within the jejunum. Ischaemia–reperfusion injury impaired gut cellularity, as demonstrated by reduced mucosal protein and DNA contents. Furthermore, ischaemia–reperfusion injury decreased the expression of CD44 mRNA and cell surface receptors. This raises the possibility that ischaemia–reperfusion injury impairs gut integrity and gut barrier function by reducing cell–cell and cell–matrix interactions. Possible explanations for these findings are that the decreased expression of CD44 is indicative of mucosal cell death due to ischaemia–reperfusion injury, or that the reperfusion period was not long enough to detect ischaemia–reperfusion injury-induced PMN infiltration.

CD44 plays an important role in biological processes such as haematopoiesis, lymphocyte activation, cellular migration, tumour progression and metastasis[15]. In addition, CD44 has been implicated in signal transduction[16], enhancement of natural killer cell cytotoxic activity[17] and regulation of murine B cell effector functions[18]. CD44 is a widely distributed cell surface glycoprotein whose principal ligand has been identified as hyaluronan, a major component of the extracellular matrix[18]. Analysis of canine epithelium in the kidney has shown that the distribution of CD44 is restricted to the basolateral domain of polarized epithelial cells, supporting the belief that CD44 plays a role in interepithelial interactions[19].

The site of expression of CD44 is of crucial importance. In normal small intestine, CD44 expression is seen on many different cells within the lamina propria. However, expression on epithelial cells is restricted to the region of cell division in the base of the crypts[20]. This distribution, combined with the established functions of CD44, suggests an involvement in the maintenance of villous integrity[3,21]. This is supported by Jun *et al.*[22] who found that CD44 expression was most prominent within tight junctions of rats with experimental glomerulonephritis.

This study showed that ischaemia–reperfusion injury decreased CD44 expression by villous epithelial cells. CD44 expression near the villous tips was first reported by Uff *et al.*[3] during small bowel allograft rejection. Such changes in the pattern of CD44 expression may be related to alterations in extracellular matrix components and loss of villous integrity. This is because a major function of the extracellular matrix is to provide structural support to the villi[20]. The extracellular matrix contains hyaluronan molecules which have large hydrodynamic volumes that are able to trap substantial amounts of water and therefore influence tissue swelling[23]. CD44 expression plays an important role in the maintenance of hyaluronan homoeostasis as demonstrated by impaired tissue repair and failure of the epidermis to undergo hyperplasia in CD44 knockout mice[24].

Cytokines may influence the expression of CD44 on villous epithelial cells. Uff *et al.*[3] suggest that alterations in the pattern of CD44 expression may be due to changes in the cytokine profile of damaged mucosa. Tumour necrosis factor (TNF) α and interferon γ have been shown to up-regulate the expression of various CD44 isoforms[25,26]. This is not surprising as these cytokines are known to play an integral role in leucocyte activation and inflammation[25–27], which are also functions of CD44. In addition, it is interesting to note that ligation of hyaluronic acid and CD44 stimulates TNF-α mRNA transcript expression[28,29].

In conclusion, on the basis of the present findings it is postulated that ischaemia–reperfusion injury may impair the gut barrier by reducing normal CD44 functions. This results in inadequate infiltration of the mucosal tissues by inflammatory cells, a loss of villous integrity and a breakdown in gut barrier function. Further studies on the interactions of CD44 and other adhesion molecules involved in cell–extracellular matrix binding may improve understanding of the mechanisms underlying failure of the gut barrier.

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High prevalence of abdominal aortic aneurysm in a primary care screening programme

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Background The mortality rate associated with ruptured abdominal aortic aneurysm (AAA) remains high. The objective of this study was to assess the feasibility of population screening for AAA.

Methods In an area with a mixed rural and industrialized population of 60 000 inhabitants, all 23 general practitioners (GPs) participated. The GPs selected from their patient lists men aged 60–80 years. Men whose condition was suitable for aortic surgery were invited for screening by a single postal letter. All men responding had aortic ultrasonography in or close to the GP surgery. Diagnosis of AAA was established when the aortic diameter was 30 mm or greater. Referral for surgery was advised for an aortic diameter of 50 mm or greater.

Results Of 2914 invitations, 2419 men had ultrasonography, resulting in an attendance rate of 83·0 per cent. A total of 2416 aortic measurements were made; 196 aortic aneurysms were diagnosed (prevalence 8·1 per cent). In 40 men the aortic diameter was over 50 mm.

Conclusion Ultrasonographic screening for AAA is feasible in a primary care setting.

The mortality rate associated with ruptured abdominal aneurysm (AAA) remains high. Survival is estimated to be only 10–20 per cent[1–5]. The incidence of ruptured AAA is increasing and this can only partially be explained by the gradual ageing of the population[6–13]. AAA causes almost 2 per cent of all deaths in men over the age of 60 years in England and Wales[14]. The mortality rate is threefold higher in men compared with women, who are affected by AAA at an age 10 years older[3,4,6,8,11,15–17]. The reported prevalence varies with the definition of AAA, the geographical area and the population.

Ultrasonography is very effective in the detection of AAA[18–20]. Screening asymptomatic individuals offers the best chance for detection and elective treatment of AAA, resulting in a substantial reduction in the incidence of rupture[21]. The risk of rupture increases with the AAA size, which therefore determines the timing of surgical intervention[2,22–25]. Elective operative repair is the standard treatment, with a perioperative mortality rate of approximately 5 per cent[26–30].

AAA causes significant mortality and morbidity in elderly men; detection of the condition is simple and accurate, and an effective treatment is available[31]. Therefore a public screening programme should be considered[14,21,32,33]. The design of a programme requires information on prevalence, health care availability and patient compliance. A study was therefore performed to assess the feasibility of an ultrasonographic AAA screening programme in a primary care setting. The main objectives were to determine the attendance rate and the prevalence of AAA in men over 60 years of age[7,33]. An upper age limit of 80 years was chosen in view of the increased mortality rate of elective AAA repair and a limited life expectancy[26,34].

Patients and methods

Three neighbouring districts in the east of the Netherlands were selected for the AAA screening study, involving a mixed rural and industrialized population of 60 000. Full participation was obtained from all 23 general practitioners (GPs), serving the inhabitants of the area.

All men aged 60–80 years were selected from the GP patient registers, a total of 3098. The GPs excluded all men who previously had AAA repair and those whose condition was judged to be unsuitable for AAA repair. The most common reasons for exclusion were respiratory insufficiency with continuous oxygen therapy, cardiac failure, disseminated malignancy and poor mental state, mostly due to advanced dementia. This resulted in exclusion of 184 selected men (5·9 per cent). The remaining men were sent a single postal invitation, which included information on AAA, ultrasonography and the screening study. The invitations were signed by the local GP and the study coordinator. A telephone number was supplied for further information and logistic arrangements. Non-responders were not contacted a second time.

Abdominal aortic investigations were carried out with a portable B-mode grey scale machine with a 3·75-MHz transducer (TOSBEE; Toshiba Medical Systems, Woerden, The Netherlands). The scanner was transported to locations adjacent or close to the GP surgeries, such as local health care buildings. Imaging was performed by one of four experienced technicians, recruited from the division of ultrasonography of the Department of Radiology, St Radboud University Hospital. The most dilated segment of the abdominal aorta was identified by longitudinal scanning from the diaphragm to the aortic bifurcation. The maximum diameter of the infrarenal and suprarenal abdominal aorta was measured in both transverse and anteroposterior directions[35,36].

A diagnosis of AAA was established when an aortic diameter of 30 mm or more was measured. Following AAA detection the GP was informed. For AAAs with a diameter of 50 mm or greater, referral to a regional hospital was advised for elective aneurysm repair. Ultrasonographic follow-up is continuing every 6 months for AAAs less than 50 mm. During follow-up, referral is advised if the aneurysm becomes symptomatic, the diameter increases to 50 mm or more and/or the growth rate is over

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10 mm/year. The study was approved by the ethics committee of St Radboud University Hospital.

Results

A total of 2914 men were invited for aortic screening. Ultrasonographic investigation was performed in 2419 cases, resulting in an attendance rate of 83·0 per cent. There was little variation in compliance between the different areas with attendance rates of 81·8, 82·3 and 84·9 per cent.

Complete aortic measurement was achieved in 2416 men (99·9 per cent). In one, urinary bladder dilatation with megaureters made visualization of the aorta impossible. In a second patient extreme obesity in combination with bowel gas interfered with measurement of the suprarenal aorta. Because of chorea a third patient was unable to maintain a supine position during the investigation. The distribution of aortic diameters is shown in *Fig. 1*. In 196 men the infrarenal aortic diameter was 30 mm or greater; the prevalence of AAA was therefore 8·1 per cent. Stratification of detected AAAs according to age did not show an increase in AAA prevalence with age (*Fig. 2*). Of the 196 AAAs detected 40 were 50 mm or greater in diameter (prevalence 1·7 per cent). The distribution of larger aneurysms was also not influenced by age. These 40 patients were referred for

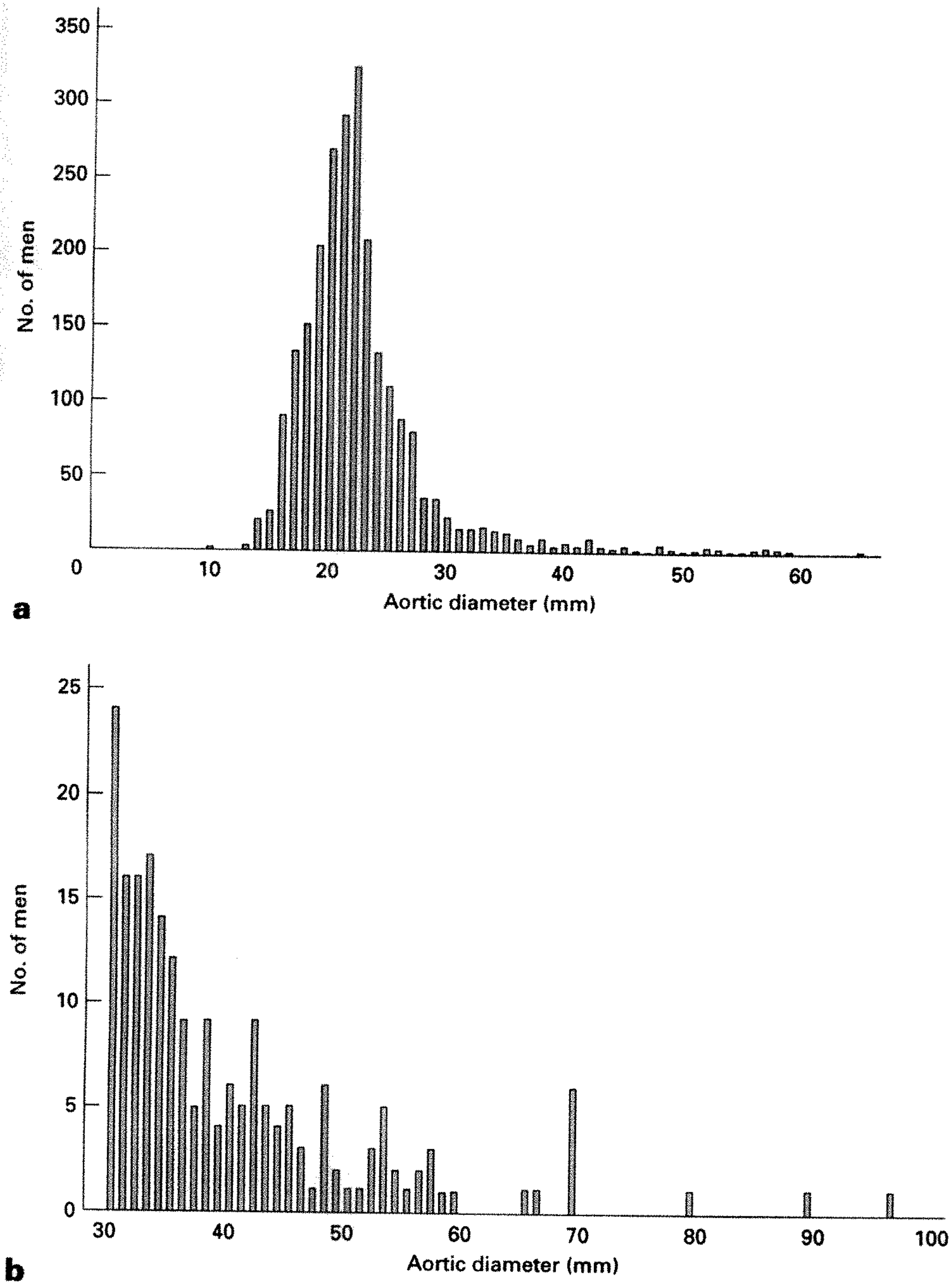

Fig. 1 a Distribution of maximum infrarenal abdominal aortic diameters in 2416 men aged 60–80 years. b Distribution of maximum infrarenal abdominal aortic diameters of 30 mm or more

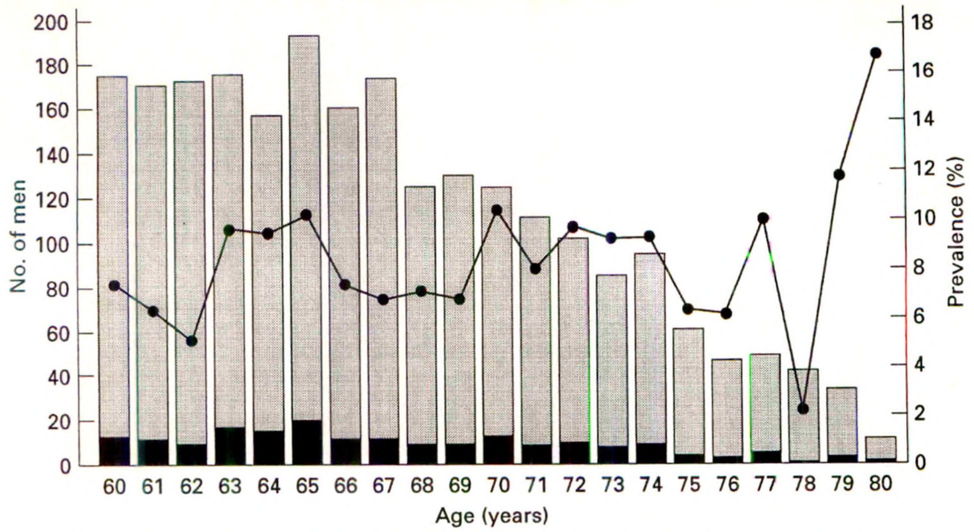

Fig. 2 Distribution of screened population ($n = 2419$) according to age. ▨, Total number of men examined by ultrasonography; ■, number of abdominal aortic aneurysms (AAAs) detected; ●, age-specific prevalence of AAAs

surgery. Two men did not have an operation; one refused elective repair after being informed about risks and the other was not thought fit enough. Thirty-eight men underwent elective aneurysm repair; one died within 30 days following wound complications and multiple organ failure. Another patient died from pneumonia 2 months after operation. Follow-up scans over 6–18 months in the 156 men with an AAA less than 50 mm in diameter have resulted in another three elective aneurysm repairs.

Discussion

This study confirms that AAA is a fairly common condition in men aged over 60 years. Direct comparison of the prevalence found in this programme with that in other reports is complicated by differences in the observed population and diverse definitions[35–37]. An analysis of the results, defining AAA as a distal aortic diameter of at least 50 per cent more than that of the proximal aortic diameter and/or an absolute infrarenal diameter of 30 mm or more, results in a prevalence of 9·7 per cent (235 of 2416). If the absolute threshold is raised to a diameter of 35 mm the prevalence decreases to 6·6 per cent. These results correspond with the outcome of other studies in open populations as shown in *Table 1*[21,38–47]. The high attendance rate in this study compares favourably with those reported from similar screening programmes, mostly conducted in the UK and Northern Europe. In other population screening studies in the

Table 1 Results of reported aortic screening programmes

Reference	Year	Age (years)	Sex	No. screened	Attendance rate (%)	Definition of AAA		Prevalence of AAA (%)	Definition of large AAA (mm)	Prevalence of large AAA (%)
						Size (mm)	Direction			
Bengtsson *et al.*[38]	1991	74	M	375	75·2	≥25	trans	10·7	≥40	3·3
Boll *et al.* (this study)	1998	60–80	M	2419	83·0	≥30	max	8·1	≥50	1·7
Collin *et al.*[39]	1988	65–74	M	426	51·7	≥30	max*	4·2	≥40	2·4
Holdsworth[40]	1994	65–79	M	628	78·5	≥30	diam	5·1	≥50	1·6
Kullmann *et al.*[41]	1992	≥60	M	1256	47·3	≥30	a.p.	7·3	≥40	1·8
Lucarotti *et al.*[42]	1993	65	M	4232	79·3	>25	a.p.	8·4	≥40	1·3
Morris *et al.*[43]	1994	≥50	M	3030	73·1	≥30	diam	5·2	≥46	1·3
O'Kelly and Heather[44]	1989	65–74	M	906	75·8	>25	a.p.	7·8	>40	1·5
Pleumeekers *et al.*[45]	1995	≥50	M	2217	78	≥35	a.p.†	4·1	≥50	0·8
		≥50	F	3066	78	≥35	a.p.†	0·7	≥50	0·1
Scott *et al.*[21]	1995	65–80	M	2342	73·1	≥30	max	7·6	≥50	1·4
		65–80	F	3052	65·2	≥30	max	1·3	≥50	0·2
Simoni *et al.*[46]	1995	65–75	M	741	58·5	≥30	max	8·8	≥40	4·3
		65–75	F	860	58·5	≥30	max	0·6	≥40	0·1
Smith *et al.*[47]	1993	65–75	M	2669	76·3	≥30	max	8·4	>40	3·0

*Disregarding the absolute aortic diameter, an abdominal aortic aneurysm (AAA) was also considered to be present when the maximal diameter of a dilated segment of the aorta was 5 mm or more greater than the proximal suprarenal aortic diameter; †disregarding the absolute aortic diameter, an AAA was also considered to be present when the maximal diameter of a dilated segment of the aorta was equal to or greater than 150 per cent of the proximal aortic diameter. trans, Transverse; max, maximum; diam, diameter (not specified according to direction of measurement); a.p., anteroposterior

Netherlands, such as for breast cancer, the compliance tends to be high in comparison with other countries. This can be attributed to population differences. Two factors in the design of the present study are considered to have contributed to the high compliance. First, the programme was actively supported by the local GPs, who also signed the invitations for screening, and second, ultrasonography was performed locally and was therefore easily accessible.

The costs of the programme ensuing from 3000 postal invitations, 2400 ultrasonographic examinations, GP reimbursement and communication amount to £75 000, corresponding to £31 per individual screened or £383 per aneurysm detected. Taking into account that 184 (5·9 per cent) of the 3098 men aged 60–80 years were not invited for AAA screening for medical reasons and the attendance rate of those who were invited was 83·0 per cent, a total of 78·1 per cent (2419 of 3098) of the population at risk was actually screened.

Primary care-based ultrasonographic screening of men aged 60–80 years in a mixed rural and industrialized population results in a high attendance rate and revealed a high prevalence of asymptomatic AAA. The screening programme was inexpensive and well received both by patients and GPs. The assumed substantial reduction of death from ruptured AAA would support the idea of a large-scale AAA screening study of the population at risk[21].

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Histological study of colonic ischaemia after aortic surgery

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Background Colonic ischaemia is a well documented complication of abdominal aortic reconstruction. In this prospective study patients had routine preoperative and postoperative colonoscopy and biopsy, in order to determine the true incidence and implications.

Methods Fifty-six patients undergoing elective infrarenal aortic surgery, 28 for aneurysm and 28 for occlusive disease, had colonoscopy and biopsy before and 1 week after operation.

Results Colonic ischaemia was identified histologically in biopsies from 16 (30 per cent) of 53 patients. Almost half the patients had normal macroscopic appearances. Two factors exhibited a statistically significant association with the development of ischaemia: prolonged cross-clamp time ($P < 0{\cdot}05$) and postoperative diarrhoea ($P < 0{\cdot}001$). Co-morbidity was much higher in patients with colonic ischaemia ($P < 0{\cdot}005$). Overall morbidity was significantly greater in the aneurysm group ($P < 0{\cdot}05$).

Conclusion Colonic ischaemia is common after aortic reconstruction. When suspected, colonoscopy with biopsy is diagnostic.

Abdominal aortic reconstruction is a routine vascular procedure, but is still associated with significant morbidity and a mortality rate approaching 6 per cent for elective aneurysm repair[1–4]. First documented in 1954[5], postoperative colonic ischaemia remains a serious potential complication; the reported incidence varies from 0 to 32 per cent[6]. Important predisposing factors are listed in *Table 1*[7–19]. The commonest reported symptom is diarrhoea with or without blood, usually commencing within 48 h of surgery[19,20]. Absence of diarrhoea is documented[18] and may present diagnostic difficulty.

The aim of this study was to examine, by colonoscopy and biopsy, the incidence of overt and subclinical postoperative colonic ischaemia in an unselected group of patients undergoing elective infrarenal aortic surgery, and to identify predictive factors.

Patients and methods

All patients undergoing elective abdominal aortic surgery involving infrarenal cross-clamping were included after giving their informed consent. Ethics committee approval was obtained before commencement of the study. Exclusion criteria were: a history of previous aortic surgery, colonic disease or resection, and intraoperative diagnosis of colonic pathology.

Venous blood was taken for measurement of baseline haematology and biochemistry. Arterial blood was sampled for measurement of blood gases, and 24-h urine collection was performed to determine creatinine clearance. The night before surgery patients were given a phosphate enema to evacuate the distal colon and rectum.

Table 1 Factors predisposing to postoperative colonic ischaemia[7–19]

Inferior mesenteric arterial ligation
Severe stenosis or occlusion of the superior mesenteric artery, internal iliac arteries or other collateral channels
Aortoiliac steal syndrome
Operative damage to vital collaterals, mesentery or colon
Previous colectomy with sacrifice of middle colic artery
Prolonged hypotension with resultant hypoperfusion
Operation for ruptured aneurysm
Embolization of atheromatous debris or cholesterol
Prolonged cross-clamp time

A standard general anaesthetic technique was used, with non-invasive monitoring of pulse, respiratory rate, tidal volume, oxygen saturation (S_{aO_2}) and end-tidal carbon dioxide. Central venous pressure and S_{aO_2} were measured directly by means of internal jugular venous and radial arterial lines, and urine output was monitored continuously.

After induction of anaesthesia, patients were placed in the left lateral position and a limited colonoscopy performed using an Olympus CF-10 L colonoscope (Olympus Optical, London, UK). Note was made of visual appearances, and biopsies were taken at 20, 30 and 40 cm from the anal verge. Specimens were immediately fixed in 10 per cent formalin solution for later examination by the same consultant histopathologist.

All operations were performed using a standard technique of aortic graft insertion. Aortic aneurysms were replaced by inlay of straight or bifurcated grafts as necessary. Aortic occlusive disease was bypassed using an end-to-side proximal anastomosis. At operation, note was made of the patency of the superior mesenteric artery (SMA), inferior mesenteric artery (IMA) and marginal arteries. Cross-clamp time was documented together with whether or not the IMA or internal iliac arteries were ligated. All patients except one had preservation of at least one internal iliac artery. The incidence of significant hypotension, defined as systolic blood pressure less than 85 mmHg lasting longer than 10 min, was documented for the intervals before, during and after cross-clamping, and after operation.

Fluid administration was governed by anaesthetic staff, losses being replaced by colloid, crystalloid and blood, as required. Routine postoperative management included intravenous fluids, analgesia using intravenous morphine via a patient-controlled administration pump, and monitoring of pulse, blood pressure, central venous pressure, urine output and peripheral pulses. The incidence of postoperative diarrhoea was documented, as were cardiac, respiratory, renal and circulatory complications.

Haematology and serum biochemistry were measured on days 1, 2, 3 and 7 after operation; 24-h urine collections were also made for the purpose of measuring creatinine clearance.

Colonoscopy with biopsies was repeated under sedation 1 week after surgery.

Results

Fifty-six patients were studied (male : female ratio 3 : 1, mean age 64 (range 46–80) years). The mean age of those

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undergoing surgery for aneurysm was significantly greater than that of patients having an operation for occlusive disease (67 *versus* 60 years; $P<0{\cdot}005$, two-tailed unpaired *t* test).

Preoperative arteriography was available in 35 patients (63 per cent), seven with an aneurysm and 28 with occlusive disease. The SMA was patent in all patients. Seven had an occluded or stenosed IMA; 27 had at least one occluded or stenosed common iliac artery; and 19 had at least one occluded or stenosed internal iliac artery.

At operation the IMA was ligated in significantly more patients in the aneurysm group (all patients *versus* ten of 28; $P<0{\cdot}05$, two-tailed Fisher's exact test). Ligation of both the IMA and an internal iliac artery was necessary in five patients.

Cross-clamp time ranged from 20 to 87 (mean 38) min, and was almost 5 min longer in the aneurysm group (40 *versus* 35 min, $P=0{\cdot}06$, two-tailed unpaired *t* test).

Significant hypotension occurred in ten patients (18 per cent), significantly more in the aneurysm group (nine of 28 *versus* one of 28; $P=0{\cdot}01$, Fisher's exact test). Mild to moderate diarrhoea occurred in 19 patients (34 per cent); three had associated bleeding, one of whom progressed to frank necrosis. The incidence was similar in aneurysm and occlusive groups (11 of 28 *versus* eight of 28). Stool culture for pathogens including *Clostridium difficile* was negative in all patients who had diarrhoea.

Colonic histology (Fig. 1)

All patients had normal macroscopic and microscopic appearances of colonic mucosa before surgery. Postoperative ischaemia was suggested on macroscopic appearances in 13 patients (25 per cent); however, four of these had oedema or pallor of the mucosa but normal histology. Ischaemia was diagnosed by microscopy in 16 patients (30 per cent). Of these, seven patients had normal mucosa macroscopically. There was no significant difference in the incidence of ischaemia between patients with aneurysm or occlusive disease (ten of 26 *versus* six of 27; $P>0{\cdot}05$, Fisher's exact test). In each patient, histological appearances of biopsies taken at the specified levels showed no differences in the distribution of ischaemia.

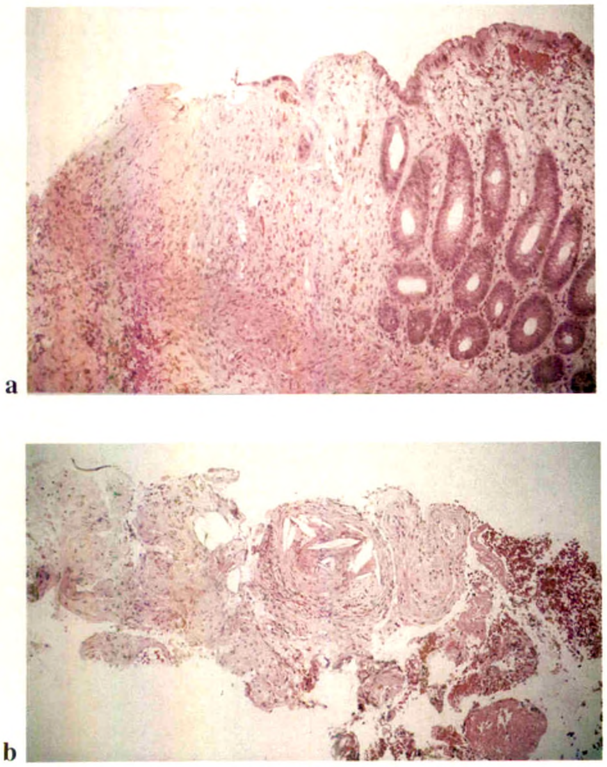

Fig. 1 a Colonic mucosa in which there is superficial ulceration and granulation tissue (to the left) along with acute inflammation of the adjacent epithelium (to the right). **b** Section from the base of the ulcer in **a** showing cholesterol emboli in the arteriole. Haematoxylin and eosin stain, original magnification ×40

Complications

Overall morbidity, excluding colonic ischaemia, was 34 per cent, significantly greater following aneurysm repair (13 of 28 *versus* six of 28 patients; $P<0{\cdot}05$, Fisher's exact test). Cardiac complications occurred in five patients (myocardial infarction, two; heart failure, two; significant dysrhythmia, one); three of these were fatal. Respiratory complications occurred in three of 56 patients (5 per cent). Three patients experienced major vascular morbidity: two had critical ischaemia of one foot which recovered, and in one patient one limb of a bifurcated graft was occluded at 24 h, requiring further surgery. There were no haemorrhagic complications. Gastrointestinal complications included one fatal colonic infarction on the ninth postoperative day and one perforated gastric ulcer on day 10, with recovery after partial gastrectomy. Most renal complications were subclinical and were diagnosed on the basis of changes in serum creatinine or creatinine clearance (30 per cent rise in the former or decrease in the latter sustained for a minimum of 2 days); all but one patient recovered within 1 week. No patient required dialysis, nor were any deaths directly attributable to renal failure.

Patients with colonic ischaemia

Comparing patients with and without colonic ischaemia, there were no differences in age, sex and preoperative arterial patencies (*Fig. 2*). At operation, a palpable pulse was noted in the IMA in nine of 16 patients who developed colonic ischaemia compared with 33 of 40 who did not ($P<0{\cdot}05$, Fisher's exact test). All patients had pulsatile marginal arteries. Although IMA ligation was performed more frequently in patients who developed

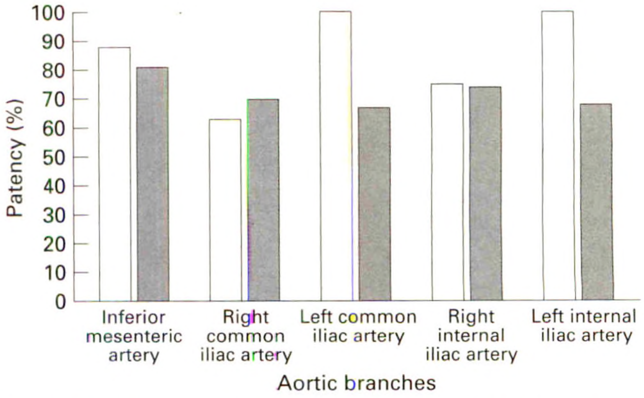

Fig. 2 Patency of aortic branches at preoperative angiography in patients with (□) and without (▨) colonic ischaemia. There were no significant differences in patency between the two groups

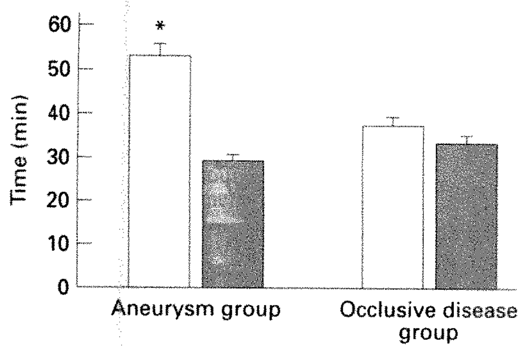

Fig. 3 Aortic cross-clamp time in patients with (□) and without (▨) colonic ischaemia. $P < 0{\cdot}05$ *versus* patients without colonic ischaemia (Mann–Whitney *U* test)

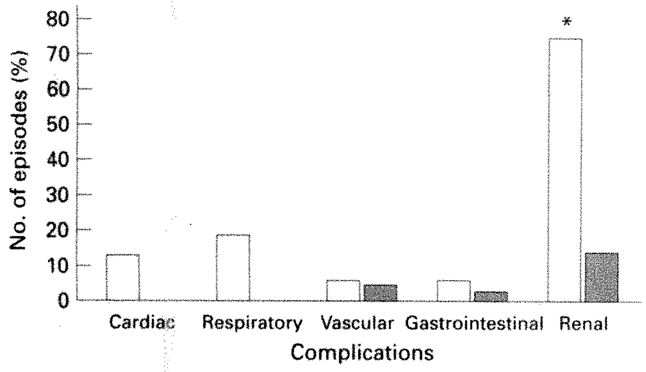

Fig. 4 Morbidity in patients with (□) and without (▨) colonic ischaemia. $P < 0{\cdot}05$ *versus* patients without colonic ischaemia (Fisher's exact test)

colonic ischaemia (13 of 16 *versus* 25 of 40), this did not reach statistical significance.

Cross-clamp time was significantly longer in patients who developed ischaemia (mean 45 *versus* 35 min; $P < 0{\cdot}05$, Mann–Whitney *U* test). This difference occurred in the patients with aneurysm (mean 53 *versus* 29 min; $P < 0{\cdot}05$) (*Fig. 3*). Significant hypotension occurred more often in patients who developed colonic ischaemia (five of 16 *versus* five of 40), although this difference was not significant. Postoperative diarrhoea occurred more often only in patients with ischaemia (14 of 16 *versus* five of 40; $P < 0{\cdot}001$, Fisher's exact test). Mortality and overall morbidity rates were also greater in the ischaemia group (13 of 16 *versus* six of 37; $P < 0{\cdot}005$, Fisher's exact test) (*Fig. 4*).

Discussion

The majority of reports about postoperative colonic ischaemia following aortic surgery are anecdotal or retrospective. Ernst *et al.*[8] colonoscoped 50 consecutive patients within 4 days of aortic surgery, noting macroscopic changes of ischaemia; Zelenock *et al.*[21] performed colonoscopy in 100 consecutive patients within 48 h of surgery. The incidence of ischaemia in these studies was 6 and 3 per cent respectively, but they relied on visual assessment by the endoscopist and these values were almost certainly inaccurate.

A more scientific method of diagnosing ischaemia is by histological examination. Marston *et al.*[22] described three patterns of ischaemic colitis: infarction of the colon, ischaemic stricture and 'transient ischaemic colitis'. Bicks *et al.*[23] also agreed with the concept of 'transient' ischaemia: diarrhoea which occurred 6–8 days after operation, with a spectrum of proctoscopic findings varying between normal, pallor, non-specific oedema, granularity, friability and punctate ulceration. Others have reported non-specific sigmoidoscopic appearances similar to those of ulcerative colitis[24,25]. Macroscopic signs of transient mucosal ischaemia may include non-specific diffuse hyperaemia with multiple submucosal haemorrhagic spots, oedema, or small erosions or ulcers[26]. It was felt that such lesions had no clinical significance. However, patients with subclinical ischaemia may develop mucosal disruption at macroscopic and microscopic levels, and may be susceptible to development of sepsis from enteric organisms and multiple organ failure.

The importance of histological assessment in the diagnosis of ischaemic colitis was emphasized by McBurney *et al.*[20]. In the present study all patients had normal macroscopic and microscopic appearances before operation. Of 13 patients (25 per cent) with abnormal postoperative macroscopic appearances, four had normal histology, therefore excluding ischaemia. However, ischaemia was diagnosed on the basis of histology in seven more patients, resulting in an overall incidence of 16 patients (30 per cent). This incidence is higher than that in any previously reported prospective study. Prospective studies that reported a high incidence of ischaemia are not comparable for various reasons: Fiddian-Green *et al.*[27] and Schiedler *et al.*[28] described incidences of 25 and 29 per cent respectively, but in selected patients considered to be at highest risk of developing colonic ischaemia. Krohg-Sorensen and Kvernebo[29] diagnosed ischaemia on the basis of symptoms in three of 16 patients (19 per cent), Meroni *et al.*[30] reported a 17 per cent incidence in only 18 patients, and a 13 per cent incidence was reported by Hagihara *et al.*[31] in a larger study.

Preoperative arteriography was not performed in most patients in this study, particularly before aneurysm repair. Although important information may be obtained[9,32] preoperative arteriography does not reduce morbidity and mortality rates[3] and in this study it failed to help predict which patients would develop postoperative colonic ischaemia.

The importance of the fate of the IMA is unknown. IMA clamping reduces colonic blood flow, particularly in patients undergoing surgery for occlusive disease[29]. Ernst *et al.*[33] described a critical IMA stump pressure of 40 mmHg, below which ischaemia would develop after IMA ligation, but in their study only one such patient had ischaemic colitis. Ernst and colleagues reported previously that colonic ischaemia may still develop when the IMA is preserved[8]. Others found that ligation of a patent IMA did not increase the likelihood of ischaemic colitis, and that IMA stump pressure measurement was unreliable[28]. Zelenock *et al.*[21] suggested that ischaemia was less likely if the IMA was reimplanted; one large retrospective study found a lower incidence of colonic infarction when a policy of routine IMA reimplantation was undertaken[6]. In the present study colonic ischaemia was more common in patients who had IMA ligation (although not significantly so). Reimplantation was never performed.

The importance of the duration of aortic clamping in the aetiology of colonic ischaemia is well recognized[19]. This is particularly important in patients with aneurysms, who do not have an adequate collateral circulation. In the present study, cross-clamp time was significantly longer in patients who developed ischaemia, mainly during aneurysm repair. The few published prospective studies disagree whether colonic ischaemia is more likely after surgery for aneurysm than for occlusive disease[8,28]. In the present study, patients who had aneurysm repair had a longer cross-clamp time and were significantly more likely to need IMA ligation. Perioperative hypotensive episodes were more frequent, diarrhoea more common and histological ischaemia more prevalent in patients who had aneurysm repair. Mortality and overall morbidity rates were also greater. Therefore, although colonic ischaemia did not develop in significantly more patients with aneurysm, risk factors for ischaemia were more common and postoperative mortality and morbidity rates were higher in this group.

Although a high incidence of colonic ischaemia was demonstrated in this study (30 per cent), progression to colonic infarction was rare; only one patient died from this complication. In this case, the patient's clinical state did not suggest that laparotomy was required. The severity of ischaemia cannot currently be predicted by histological means alone.

While in many cases, colonic ischaemia is truly transient and is not a major clinical problem, patients who have prolonged aortic cross-clamp, or who develop postoperative diarrhoea, would benefit from investigation. Sigmoid tonometry, which can detect intramural acidosis and thus ischaemia, might help determine which patients should undergo colonoscopy. When colonoscopy is deemed necessary, biopsy and histology should be performed. Although current basic histological stains do not fulfil any predictive role, a diagnosis of ischaemia is indicative of higher risk.

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Comparison of duplex imaging and arteriography in the evaluation of lower limb arteries

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Background The aim of this study was to assess the accuracy of duplex imaging, compared with arteriography, in detecting arterial disease distal to the renal arteries.

Methods Some 177 legs were studied in 90 patients (59 men, 31 women; median age 68 years) with peripheral arterial disease. Each patient had conventional intra-arterial angiography and duplex ultrasonography. Each leg was divided into 17 arterial segments, and the disease in each segment was quantified by measuring the peak systolic velocity ratio across any arterial lesion that was identified.

Results Compared with angiography, duplex imaging was able to detect arterial disease with an overall sensitivity of 92 per cent, specificity of 99 per cent, positive predictive value 91 per cent and negative predictive value 100 per cent, and with a κ value of 0·87 (95 per cent confidence interval (c.i.) 0·81–0·93). Duplex was able to determine the length of the arterial lesion with a sensitivity of 89 per cent and a specificity of 98 per cent with a κ value of 0·88 (95 per cent c.i. 0·86–0·90). When the surgeon's final management decision concerning each vascular lesion was used as the reference, duplex and arteriography were equivalent, with an accuracy of 84 per cent and 85 per cent respectively in identifying the management used.

Conclusion Duplex ultrasonography is reliable in detecting arterial lesions in peripheral arteries and could be used routinely in the initial evaluation of patients with lower limb arterial disease.

Arteriography has been regarded as the standard investigation for peripheral arterial disease[1]. Arteriography gives an anatomical representation but does not assess the functional obstruction presented by stenotic lesions. Recently duplex ultrasonography has replaced arteriography for investigation of carotid artery disease[2]. The use of duplex imaging to assess peripheral arterial stenoses, using the peak systolic velocity ratio (PSVR) across the lesion, has been described[3–5] and is reliable in the aortoiliac and femoropopliteal regions in comparison with arteriography[6–9]. In the intervening years there have been several technical improvements in duplex imaging equipment.

The aim of this study was to assess the accuracy of duplex imaging in detecting and assessing the severity and extent of lesions in the peripheral arterial tree in comparison with arteriography. A further aim was to assess the concordance of the clinical decision concerning patient management based on duplex results with that based on arteriography.

Patients and methods

Arterial duplex imaging and intra-arterial digital subtraction arteriography (IADSA) were performed in 90 patients (177 legs in 59 men and 31 women of median age 68 years). Eighty-one patients had intermittent claudication, one had ischaemic ulceration, and eight had rest pain. Ethics committee approval for this study was obtained from the University College London Medical School Ethics Committee and patients gave their written consent.

Duplex imaging was done by one of two trained vascular technologists who were unaware of the results of angiography. An Acuson scanner 128XP/10v (Acuson, Mountain View, California, USA) was used. A 2.5-MHz curvilinear and a 7-MHz linear array probe were used to examine the pelvic and the infrainguinal vessels respectively.

All patients fasted for 6 h before imaging to minimize the presence of bowel gas. With the patient supine, imaging was done from the infrarenal aorta to the ankle vessels. Colour flow was used to outline the arterial wall and any arterial lesions, and for each arterial segment the peak systolic velocity was obtained. The PSVR of any stenosis was derived by comparing the peak systolic velocity at the stenotic area to that of the prestenotic or poststenotic area. A PSVR of 2·0 was used to differentiate between a significant stenosis with more than 50 per cent reduction in luminal diameter and an insignificant stenosis with less than this. For the assessment, the peripheral arterial vessels were divided into 17 segments: common iliac, external and internal iliac, common femoral, superficial femoral and profunda femoris. The superficial femoral artery was divided into proximal, mid and distal segments, while the popliteal was divided into proximal and distal, and each crural vessel into proximal and ankle segments.

The length of iliac disease was determined by using the duplex ultrasonography measuring calliper; for femoropopliteal lesions a non-permanent skin marker was used to mark the proximal and distal ends of the arterial lesion detected by duplex imaging, and the distance between them was measured with a ruler.

IADSA was done within a week of duplex imaging by a consultant radiologist who was unaware of the duplex findings, using the Seldinger technique. A 7-Fr sheath was introduced through the common femoral artery, then a 5-Fr catheter was placed through the sheath to the aorta. Intra-arterial pressure measurements were not done routinely and only uniplanar views were obtained. The severity of stenosis was determined by dividing the diameter of the lumen by the diameter of the nearest normal segment. All IADSA films were reviewed and classified by two consultant radiologists separately. The length of the iliac

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and femoropopliteal stenoses and occlusions were measured from the IADSA investigation.

To assess the clinical benefits and diagnostic reliability of duplex imaging compared with IADSA, five vascular surgeons were given 164 anonymous coded duplex and IADSA reports at two different sessions (6-month interval). All these reports were supported with a brief clinical history. Surgeons were asked to make a management decision based on either the arteriography or duplex reports.

The treatment that each patient received was established from the clinical notes and was used as the reference standard. The clinical decisions were classified into: conservative, balloon angioplasty, bypass surgery, combined therapy (balloon angioplasty and bypass surgery), thrombolysis or sympathectomy.

Statistical analysis

The sensitivity and specificity of duplex imaging compared with arteriography in detecting a non-significant (less than 50 per cent) and a significant (greater than 50 per cent) lesion or occlusion were calculated. The kappa (κ) statistic was computed to measure the level of agreement between the radiologists and technologists. For agreement by chance alone the κ value is 0 and for perfect agreement the κ value is 1. The 95 per cent confidence interval of κ values was also calculated.

Results

Some 3108 arterial segments in 177 legs (630 aortoiliac segment, 531 femoral, 885 femoropopliteal and 1062 run-off vessels in both calf and ankle) were examined in 90 patients. A total of 466 arterial lesions was identified and graded on arteriography, compared with 451 lesions identified and graded on duplex imaging. *Table 1* demonstrates the distribution of the arterial lesions in a two-way table of duplex and IADSA data.

In the aortoiliac region 570 of 630 segments were normal on both duplex and arteriography. Of 90 patients, two examinations of the iliac vessels were described as ‘difficult’ (because of the presence of bowel gas in one and obesity of the other patient; the common iliac artery and its bifurcation were not clearly seen). In the femoral artery 485 of 531 arterial segments were normal on both duplex scan and arteriography. Duplex was able to identify significant stenoses in the femoral arterial segment with a sensitivity and a specificity of 100 and 99 per cent respectively; for occlusions the sensitivity and specificity were 100 and 99 per cent (overall sensitivity and specificity in *Table 2*).

In the femoropopliteal region 648 segments were normal by both modalities. Some 213 arterial lesions were identified by both IADSA and duplex imaging. At the level of the run-off vessels 915 of 1062 segments were normal; 37 significant stenoses and 68 occlusions were recognized by both methods of investigation.

Table 1 Two-way table demonstrating the overall agreement between duplex imaging and arteriography

	Grading of IADSA based on diameter reduction (%)					
PSVR	Normal	< 20	20–< 50	50–99	Occlusion	Total
1	2618	8	2	10	19	2657
< 1·5	1	5	4	1	0	11
1·5–< 2	0	1	4	4	0	9
2	11	1	3	120	6	141
No pulse	12	0	0	6	272	290
Total	2642	15	13	141	297	3108

PSVR, peak systolic velocity ratio

Table 2 Statistical assessment of duplex imaging compared with intra-arterial digital subtraction angiography for all arterial segments

Artery	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	κ
AI	89	99	92	99	0·81 (0·92–0·70)
FA	100	99	95	100	0·94 (0·99–0·89)
FP	95	99	94	99	0·92 (0·94–0·90)
ROF	82	99	82	100	0·81 (0·87–0·75)
Overall	92	99	91	100	0·87 (0·93–0·81)

Values in parentheses are 95 per cent confidence interval. PPV, positive predictive value; NPV, negative predictive value; AI, aortoiliac; FA, femoral artery; FP, femoropopliteal region; ROF, run-off vessels

A summary of the overall accuracy of duplex scanning in all segments is shown in Table 2. Although a PSVR of 2·0 was used prospectively to discriminate between significant and insignificant stenosis, on receiver–operator curve (ROC) statistics, a PSVR of 1·8 was more sensitive in identifying a significant stenosis (*Fig. 1*).

Duplex and length of the arterial lesions

Some 807 arteries in 177 legs of 90 patients were examined (630 aortoiliac and 177 femoropopliteal). No disease was found in 624 arterial segments (559 aortoiliac and 65 femoropopliteal). Some 152 arterial lesions were detected by both methods of investigation (44 aortoiliac and 108 femoropopliteal), 89 lesions less than 5 cm in length (44 aortoiliac and 45 femoropopliteal), 31 lesions of 5–10 cm, and 32 lesions of more than 10 cm. Duplex imaging showed a sensitivity of 89 per cent, specificity of 98 per cent, positive predictive value of 92 per cent and

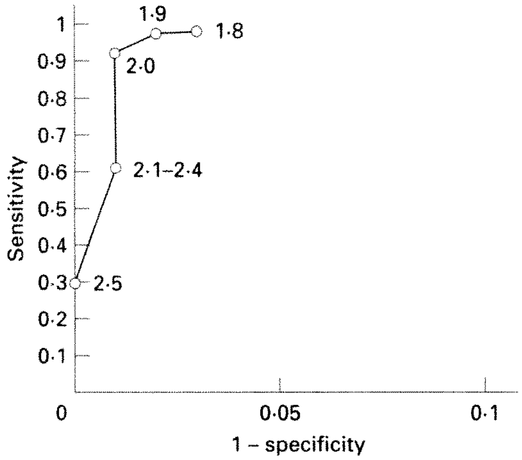

Fig. 1 Receiver–operator curve demonstrating the accuracy of various values of peak systolic velocity ratio (PSVR) in identifying significant stenosis. A PSVR of 1·8 is the most sensitive point for discriminating between significant and insignificant stenosis

Table 3 Accuracy of the decision based on duplex imaging compared with intra-arterial digital subtraction angiography when the actual treatment the patient received was used as a reference standard

		Accuracy					
Reference standard	Test	Surgeon 1	Surgeon 2	Surgeon 3	Surgeon 4	Surgeon 5	Mean
Final treatment received	Duplex	93	78	79	83	87	84
Final treatment received	IADSA	90	83	77	80	95	85
Decision based on IADSA	Duplex	98	89	88	85	95	91

IADSA, intra-arterial digital subtraction angiography

negative predictive value of 97 per cent compared with IADSA (reference standard) and κ value of 0·88 (95 per cent confidence interval 0·86–0·90).

Duplex and clinical decision

When the actual treatment the patient received was used as a reference standard, the mean accuracy of the clinical decision reached by the five vascular surgeons based on duplex data was 84 per cent and the accuracy based on IADSA was 85 per cent. When the surgeons' decision based on IADSA was used as the reference standard, the mean accuracy of duplex imaging was 91 per cent (*Table 3*).

Discussion

Arteriography continues to play a central role in the diagnosis and management of arterial disease. Despite advances in catheter design, contrast materials and techniques, arteriography remains invasive and carries both morbidity and mortality risks[9]. Recently, duplex imaging has reduced the indications for arteriography in the routine assessment of carotid artery disease and bypass graft patency. The relationship between the arterial diameter and age of the subject has been established by Jager *et al.*[3], who also reported that the peak aortic velocity decreases with age. Although arteries tend to be smaller in women, the arterial flow velocities are not significantly different between the sexes. PSVR is a valuable parameter in determining the degree of arterial stenosis in leg arteries. In many reports a PSVR of 2·0 was used to discriminate between a lesion with more than 50 per cent and that with less than 50 per cent reduction in diameter[3–5,10–13].

Previously, Kohler *et al.*[4] reported that duplex imaging had a sensitivity of 82 per cent and a specificity of 92 per cent, but admitted difficulty in detecting lesions distal to a critical stenosis or occluded segment. Cossman and colleagues[5] examined 84 legs and reported that duplex imaging has a sensitivity and a specificity of 87 and 99 per cent respectively. In the present study, by further retrospective assessment of the data using ROC statistics, a PSVR of 1·8 was more sensitive in identifying significant stenosis (sensitivity 98 per cent and specificity 97 per cent). Legemate *et al.*[6–9] used a PSVR of 2·5 to define a significant stenosis (sensitivity and specificity 84 and 96 per cent respectively) but reported that in some segments (femoropopliteal) a sensitivity of only 60–70 per cent was achieved.

Occasionally duplex ultrasonography is unable to differentiate between a very tight stenosis (99 per cent diameter reduction) and total occlusion. In this study five tight stenotic lesions (one iliac and four infragenicular) on IADSA reported as occluded on duplex imaging, while three tight iliac stenoses reported on duplex were occluded on IADSA. Similar observations have been reported by Legemate *et al.*[6–9] and Sensier *et al.*[14]. Duplex ultrasonography has a similar difficulty in differentiating between a tight carotid artery stenosis and occlusion[15]. In high-grade stenoses the flow velocity falls to a low level and may be undetected, unless the Doppler detecting system is adjusted correctly by the investigator.

In the present study, the reliability of duplex imaging in delineating the severity of lower limb arterial disease and its implications on the management strategy were established. Obesity and bowel gas can reduce visualization of the iliac arteries. Few studies[16,17] have investigated the efficacy of duplex imaging of infrageniculate disease (an overall sensitivity of 75 per cent and specificity of 95 per cent). In the present study the accuracy of duplex imaging was reduced compared with that of more proximal segments (sensitivity 82 per cent and specificity 99 per cent). Distal vessels are small making them difficult to identify and assess, and calcification causes further problems by reducing the Doppler signal.

Management of the ischaemic leg is a subject of great debate. Although intermittent claudication is relatively benign, about 7 per cent of patients will develop critical limb ischaemia within 1 year[18–23]. The indications for intervention vary between surgeons. For example, in this study, a 53-year-old man had right calf pain due to a 3-cm common femoral artery occlusion shown on both duplex and IADSA (claudication distance 400 yards). Two surgeons suggested no intervention while the other three recommended balloon angioplasty. The ideal lesion for balloon angioplasty is a short iliac artery stenosis rather than a long femoropopliteal occlusion. However, the precise limits of technical feasibility and success of balloon angioplasty in the hands of interventional radiologists in different anatomical situations are still matters for debate. It is not surprising that surgeons disagreed to some extent when presented with the same data, especially in the isolation of a non-clinical study when the patients were not available for clinical examination.

Some vascular surgeons make management decisions based on duplex imaging alone. Elsman *et al.*[24] reported that 36 of 100 patients underwent angioplasty without any diagnostic arteriography and in 62 patients the treatment strategy could be determined without diagnostic arteriography. The present data support this viewpoint; the accuracy of clinical decision based on duplex imaging compared with that based on IADSA was 94 per cent. This suggests that preoperative arteriography provides no additional diagnostic benefit over duplex ultrasonography. Duplex imaging is an accurate, non-invasive method for the routine assessment of lower limb arterial disease.

Management decisions can be made safely from the information provided by duplex imaging alone.

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Evidence that aminoguanidine inhibits endotoxin-induced bacterial translocation

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Background The role of inducible nitric oxide synthase (iNOS) in endotoxin-induced bacterial translocation was investigated by using its specific blocker aminoguanidine in 46 albino mice (25–35 g) allocated into four groups.

Methods The first group received intraperitoneal saline (control; 0·9 per cent w v^{-1} sodium chloride 1 ml kg^{-1}; $n = 6$), the second group intraperitoneal endotoxin (*Escherichia coli* lipopolysaccharide 055:B5 20 mg kg^{-1}; $n = 19$), the third group intraperitoneal aminoguanidine (20 mg kg^{-1}, 20 min before and 12 h after saline; $n = 6$) and the fourth group both endotoxin and aminoguanidine intraperitoneally ($n = 15$). Some 24 h later, the animals were anaesthetized with ether and blood samples were collected by cardiac puncture together with mesenteric lymph node (MLN), spleen and liver specimens under aseptic conditions. Specimens were then cultured to determine the presence of colony-forming units as an index of bacterial translocation.

Results No bacterial growth was detected in samples from the first and third groups. Colony-forming bacteria were found in ten of 14 MLN samples, eight of 14 spleens, four of 14 livers and three of 14 peripheral blood samples in the second group, with *E. coli* being the predominant pathogen. In contrast, in the fourth group, colony-forming bacteria were found in only three of 14 MLN samples ($P = 0{\cdot}02$ *versus* the second group), three of 14 spleens and one of 14 liver specimens. None of the values in the fourth group was significantly different from those in the saline control group.

Conclusion The inhibition of iNOS during endotoxaemia by its specific blocker aminoguanidine attenuates the incidence of bacterial translocation in mice. These results may be exploited clinically for the prophylaxis and treatment of septic states.

In contrast to significant improvements in the care of critically ill patients, septic shock still remains a leading cause of death in non-coronary intensive care units[1]. The development of multiple organ failure during the progression of this sepsis-triggered clinical entity increases the mortality rate from 30 to 100 per cent[2]. Although Gram-positive micro-organisms[3], some fungi[4], bacterial DNA or active synthetic oligonucleotides[5] can initiate the cascade of events that leads to septic shock and multiple organ failure, it is widely accepted that sepsis and its consequences are caused predominantly by Gram-negative bacteria[4,6] and their endotoxins[7]. Endotoxin is probably the primary initiator of septic shock. A large proportion of patients with non-Gram-negative sepsis have endotoxaemia[8] and 40 per cent of patients with septic shock lack any pathogenic micro-organisms in the blood or tissue[9–11]. Since the gastrointestinal tract is the main source of endotoxin[12], it is postulated that an increase in intestinal mucosal permeability, for example resulting from blunt multiple trauma[13], burn injury[14], intestinal ischaemia and reperfusion[15], food deprivation[16] or exogenously introduced endotoxin *per se*[17], may result in the pathological migration of live bacteria into the bloodstream as well as to gut-associated lymphoid structures[18]. This may lead to fatal multiple organ failure[19].

Recent studies have revealed the mechanisms of action of endotoxin[11], and nitric oxide appears to have the central role[20]. Briefly, endotoxin, together with cytokines (e.g. interleukin 1, tumour necrosis factor, interferon γ), leads to the induction of inducible nitric oxide synthase (iNOS) in the endothelium, macrophages and vascular smooth muscle cells[21]. This results in the production of copious amounts of nitric oxide[22], which renders the vasculature hyporesponsive to vasoconstrictors[23] and vasodilators[24], resulting in refractory hypotension and diminished blood flow to vital organs, which leads to multiple organ failure[25].

Aminoguanidine, a molecule containing the guanidino group of L-arginine linked to hydrazine, is reported to be a relatively selective inhibitor of iNOS. In animal experiments aminoguanidine attenuates circulatory failure and improves survival in experimentally induced Gram-negative[26] and Gram-positive[27] septic shock. It is also possible that iNOS inhibition may reduce endotoxin-induced bacterial translocation since endotoxin-induced cellular injury is closely associated with iNOS induction[28]. In addition, endotoxin-induced intestinal microvascular leakage in the small and large intestine can be blocked by iNOS inhibition[29]. On the basis of these findings, the effects of iNOS inhibition by its specific blocker aminoguanidine were studied on bacterial translocation in experimental endotoxaemia in mice.

Materials and methods

Forty-six albino mice were divided into four groups. The first group, which served as control, received intraperitoneal saline

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(0·9 per cent w v^{-1} sodium chloride 1 ml kg^{-1}; $n = 6$); the second, intraperitoneal endotoxin (*Escherichia coli* lipopolysaccharide 055:B5 20 mg kg^{-1}; Sigma, St Louis, Missouri, USA) ($n = 19$); the third, intraperitoneal aminoguanidine (aminoguanidine hemisulphate 20 mg kg^{-1}; Sigma) 20 min before and 12 h after saline ($n = 6$); and the fourth group both intraperitoneal endotoxin and aminoguanidine ($n = 15$), complying with the relevant treatment protocols of the second and the third groups.

Twenty-four hours later, surviving animals were anaesthetized with ether, a thoracotomy was performed under aseptic conditions and blood samples were collected by sterile cardiac puncture. A 1-ml sample of blood from each animal was placed into a blood culture bottle containing brain heart infusion (BHI) broth for aerobic growth and the bottles were incubated for 7 days at 37°C. Subsequent subcultures were performed using blood agar base (Merck, Rahway, New Jersey, USA) after 48 h and eosin–methylene blue agar (EMB; Merck) after 7 days.

To obtain mesenteric lymph node (MLN), spleen and liver specimens, a midline laparotomy incision was performed. MLNs, spleen and liver were removed, weighed and homogenized in 2 ml BHI broth with grinding rods. Homogenates were placed on EMB and blood agar. After 24 and 48 h of aerobic incubation at 37°C, the plates were examined and bacteria identified using standard microbiological techniques.

All surgical interventions and preparation of the tissues were conducted under aseptic conditions with strict adherence to sterility.

Statistical evaluation was done using Fisher's exact test and differences were accepted as statistically significant when the two-tailed P value was less than 0·05.

Results

Five of 19 mice in the second (endotoxin only) group and one of 15 mice in the fourth (endotoxin plus aminoguanidine) group died within 24 h; no death was observed in the other groups. Statistical analysis indicated no significant difference in survival between the groups.

No colony-forming bacteria could be isolated from any of the samples obtained from surviving animals in the first (saline control) or the third (aminoguanidine only) group which indicated the absence of bacterial translocation in these mice (*Table 1*).

However, in the second group, colony-forming bacteria were isolated from both blood and tissue specimens. The incidence of bacteria isolated MLNs and spleen was significantly greater than that for the first group ($P = 0·01$ for MLNs and $P = 0·04$ for spleen) (*Table 1*). Although fewer colony-forming bacteria were isolated from samples obtained from the fourth group in comparison to the second, these differences were not statistically significant except for MLNs ($P = 0·02$). The predominant bacteria isolated were *E. coli*, which was present in all of the samples; *Proteus mirabilis* and diphtheroids were also encountered occasionally.

Table 1 Incidence of colony-forming bacteria as an indicator of bacterial translocation in blood and tissue specimens

	Specimen			
Group	Mesenteric lymph nodes	Spleen	Liver	Blood
Control (saline) ($n = 6$)	0	0	0	0
Endotoxin ($n = 14$)	10*	8*	4	3
Aminoguanidine ($n = 6$)	0	0	0	0
Endotoxin plus aminoguanidine ($n = 14$)	3†	3	1	0

n, Number of surviving animals after 24 h. *$P < 0·05$ *versus* control (saline) group; †$P = 0·02$ *versus* endotoxin group (Fisher's exact test)

Discussion

In this study exogenously applied endotoxin caused bacterial translocation into MLNs, spleen, liver and blood in albino mice. Aminoguanidine treatment reduced bacterial translocation. Although the differences between the values in spleen, liver and blood were not statistically significant, significant inhibition ($P = 0·02$) of bacterial translocation into the MLNs by aminoguanidine was the main finding of this study. This agrees with the concept of iNOS inhibition being beneficial in various models of septic shock[25,27].

The precise mechanism of aminoguanidine-induced inhibition of bacterial translocation is not clear. Although the selective[30] blockade of excess nitric oxide production via inhibition of iNOS[31] appears to be the main mode of action, the inhibition of polyamine catabolism[32], catalase activity[33], histamine metabolism[34] or formation of glycosylation end-products[35] may also contribute to its beneficial effects. Other possible explanations include that gastrointestinal mucosa is highly susceptible to hypoxia and ischaemia–reperfusion injury[36], and the possibility of bacteria escaping and migrating from the lumen into the bloodstream after intestinal epithelial lining disruption[2] as documented in mechanically ventilated patients[37].

In the gastrointestinal tract, endogenous nitric oxide plays an important role in the regulation of mucosal blood flow and helps mucosal protection against endotoxin-induced damage[38]. Since at least three types of nitric oxide synthase exist with diverse physiological and pathophysiological roles[39], the beneficial role of non-specific nitric oxide synthase blockage during low-perfusion states such as myocardial ischaemia[40] or septic shock[41] is questionable. By using L-arginine analogues such as N^G-nitro-L-arginine methyl ester[42] or N^G-monomethyl-L-arginine[43] during endotoxaemia, it is reported that the mortality rate is increased because of organ ischaemia and microvascular thrombosis[44]. On the other hand, there is growing evidence that selective inhibition of iNOS using aminoguanidine is beneficial by blocking the endotoxin-induced decrease in mesenteric blood flow[45], by restoring vascular responsiveness in the lungs and kidneys[46] and by inhibiting endotoxin-induced vascular leakage[47]. These reports are further supplemented by a recent study which demonstrated that aminoguanidine attenuates hepatocellular injury, respiratory dysfunction, metabolic acidosis, circulatory failure and death induced by lipoteichoic acid and peptidoglycan in an experimental model of Gram-positive shock[27]. The present results agree with current understanding of the cascade of events that lead to endotoxin-induced death and provide evidence for the attenuation of endotoxin-induced bacterial translocation by a selective iNOS blocker[48].

The concept of bacterial translocation itself remains controversial within the context of this study[49]. Despite some opposing views[50,51] there is enough evidence for its occurrence and its close association with multiple organ failure encountered during numerous states such as haemorrhagic shock[52], thermal injury[53], intestinal obstruction[54], total parenteral nutrition[55] or elective operation[56]. It is widely accepted that any injury (including exogenously applied endotoxin[17,29]) that disrupts the integrity of intestinal mucosa may facilitate the migration of bacteria out of the lumen[49] which then triggers the complex interactions between immunological defence mechanisms and invading pathogens. In the present study, the presence of colony-forming bacteria in the MLNs, spleen, liver and blood of mice that received endotoxin only is in full agreement with current understanding of the effects of endotoxin on gut-associated organ systems.

Taken together with previous results, the outcome of the present study allows a conclusion that exogenously applied *E. coli* endotoxin causes the presence of bacteria in gut-associated organs. Aminoguanidine, a relatively selective inhibitor of iNOS, attenuates this phenomenon. This action could constitute the basis for treatment of patients with systemic inflammatory response syndrome, sepsis and septic shock.

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Surgical endoscopic techniques in the diagnosis and follow-up of patients with lymphoma

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Background In patients with lymphoma, tissue for histology can be obtained through image-guided techniques or by surgery. The aim of this study was to assess the efficacy of surgical endoscopic techniques in obtaining adequate tissue specimens.

Methods Ninety-two patients with suspected or confirmed lymphoma were referred for a surgical biopsy of a deeply located intrathoracic or intra-abdominal mass or lymph node. The 86 patients who had surgery using a surgical endoscopic technique were included in this study. There were 54 men and 32 women, of mean age 34 (range 15–78) years. Most were selected directly for surgery while five previously had a failed computed tomography-guided biopsy. A total of 89 procedures were performed in 86 patients: laparoscopy (15 patients), thoracoscopy (61) and mediastinoscopy (13).

Results No patient died. One intraoperative complication occurred during thoracoscopy (1 per cent). Two postoperative complications were noted (2 per cent). Three patients required conversion to open surgery (3 per cent). Adequate tissue for histology was obtained by surgical endoscopic procedures in 87 per cent. Twelve of 13 mediastinoscopies were successful. After thoracoscopy, the success rate was 92 per cent but only nine of 15 laparoscopies were considered successful.

Conclusion In patients with lymphoma, surgical endoscopic techniques have a high diagnostic yield and a low morbidity rate. Barring exceptional circumstances these should be favoured rather than conventional open surgery.

Obtaining adequate tissue specimens is a preliminary and essential step in the diagnosis and management of patients with lymphoma. Although image-guided needle biopsies (IGNBs) have a high diagnostic yield ranging from 65 to 85 per cent[1–6], they produce insufficient specimens for specialized studies like immunophenotyping or cytogenetic analysis. The good results of IGNB reported in some large radiological series are usually presented as having an overwhelming advantage compared with the morbidity and cost of open surgery. The potential of surgical endoscopy in the diagnosis and management of lymphoma is seldom reported[7–10], so that surgical endoscopy is not yet thought as an alternative to IGNB, even in recent radiological publications[1,3].

The aim of this study was to review the efficiency of surgical endoscopic techniques in obtaining adequate specimens in patients with lymphoma, either at presentation of the disease, or at progression.

Patients and methods

Between 1991 and 1996, 92 patients presenting with suspected or confirmed lymphoma were referred for a surgical biopsy of a deeply located intrathoracic or intra-abdominal mass or lymph node (*Table 1*). Only the 86 patients who had surgery using a surgical endoscopic technique were included in this study. There were 54 men and 32 women with a mean age of 34 (range 15–78) years. Most were selected directly for surgery but five previously had a failed IGNB. During the same interval, 82 IGNBs were performed at this institution.

The different techniques used are summarized in *Table 2*. Of the six patients who had conventional open surgery, four had previous open surgery preventing laparoscopy and two needed mediastinotomy because of contraindications to split lung ventilation for thoracoscopy.

Table 1 Indication for biopsy in 86 patients

Site	No. of patients
Abdominal tumour	3
Abdominal lymph node mass	11
Mediastinal mass	31
Mediastinal lymph node mass	19
Pulmonary tumour	5
Pulmonary nodule	17
Total	86

Table 2 Procedures performed ($n = 89$)

	No. of procedures
Surgical endoscopic technique	
Laparoscopy	15
Thoracoscopy	61
Mediastinoscopy	13
Conventional open technique	
Laparotomy	3
Thoractotomy	0
Sternotomy	0
Mediastinotomy	3

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The indications for biopsy were as follows: for diagnosis in suspected but unproved lymphoma (48 patients); at progression of lymphoma, e.g. recurrence at a new site (23 patients); or for restaging on completion of medical treatment; in patients with a residual mass, the concern was to determine whether there was persistent disease (15 patients).

Technical aspects

Laparoscopy was initially performed with the patient supine. Reaching retroperitoneal tumours and/or latero-aortic lymph nodes was often difficult using this position, so the lateral position was adopted, which allows the intestines to drop away, facilitating the approach to the retroperitoneal vessels. Patients were discharged 1 or 2 days after surgery.

Thoracoscopy was performed using double-lumen tracheal intubation except in patients with narrowing of the trachea related to the lymphoma or a poor respiratory function contraindicating split ventilation[11,12]. In 11 patients with a small lung nodule, preoperative hook-wire localization was used[13].

Mediastinoscopy was performed using a conventional or video mediastinoscope. Whenever possible a whole lymph node was removed. Mediastinoscopy was performed either as a day case or with a single overnight stay in hospital. In the case of mediastinal tumours or lymph nodes, the indications for using either mediastinoscopy or thoracoscopy were obvious in most patients. For instance, tumours or lymph nodes in the posterior and/or inferior mediastinum could be reached only via the thoracoscope. Paratracheal lymph nodes were usually approached via mediastinoscopy. However, thoracoscopy was preferred for lesions of the upper third of the middle mediastinum, when multiple biopsies were required, such as for restaging lymphoma or biopsy of other organs, e.g. lung. Cosmetic considerations in some young women influenced choice in favour of thoracoscopy, since two or three lateral punctures are more easily hidden than a neck scar.

The study comprised 86 patients in whom 89 endoscopic procedures were performed. Clinical data, operative details and pathological results were entered prospectively into a database. A procedure was considered successful when it provided sufficient tissue for the pathologist to allow rational treatment. A small biopsy that allowed a pathological diagnosis, i.e. Hodgkin's or non-Hodgkin's lymphoma, but which did not permit subtyping was considered a partial failure. A biopsy that did not result in any diagnosis was considered a complete failure.

Results

There were no deaths. One intraoperative complication occurred during thoracoscopy (1 per cent): a pulmonary haemorrhage during lung biopsy could not be controlled thoracoscopically and required thoracotomy. The postoperative course was uneventful. Two postoperative complications were noted (2 per cent): one pleural effusion that did not need chest drainage and settled after physiotherapy and one intra-abdominal abscess following laparoscopy. In the latter case laparotomy was required but no cause for the abscess was found. It was assumed

Table 3 Subtypes of lymphomas and Hodgkin's disease by biopsy at first endoscopic operation

	No.
Non-Hodgkin's lymphoma	31
Inconclusive	4
Low-grade folicular	1
Diffuse large cell	20
Other (including lymphoblastic)	6
Hodgkin's disease	22
Nodular sclerosing	18
Mixed cellularity	4

Table 4 Outcome of patients with failure at first operation

Patient	Site of biopsy	First procedure	Result	Reoperation	Result	Final diagnosis
Total failure						
1	Abd. LN	Laparoscopy	Failure	—	—	None
2	Med. LN	Mediastinoscopy	Non-specific LN	Thoracoscopy	Success	Hodgkin's
3	Abd. LN	Laparoscopy	Failure	Laparoscopy	Success	NHL
4	Med. LN	Thoracoscopy	Failure of split ventilation	Mediastinoscopy	Success	Hodgkin's
5	Med. tumour	Thoracoscopy	Necrotic tissue	—	—	Carcinoma
6	Lung tumour	Thoracoscopy	Insufficient biopsy	Thoracotomy	Success	Hodgkin's
7	Abd. LN	Laparoscopy	Technical problem	Laparotomy	Success	Hodgkin's
8	Lung nodule	Thoracoscopy	Split ventilation impossible	—	—	None
Typing failure						
1	Med. tumour	Thoracoscopy	Small size biopsy	Mediastinoscopy	Success	Hodgkin's
2	Abd. LN	Laparoscopy	Small size biopsy	—	—	NHL without subtyping
3	Abd. LN	Laparoscopy	Small size biopsy	—	—	NHL without subtyping
4	Abd. LN	Laparoscopy	Small size biopsy	Laparoscopy	Success	NHL

Med., mediastinal; Abd., abdominal; LN, lymph node; NHL, non-Hodgkin's lymphoma

Table 5 Final pathological diagnosis after thoracoscopy in 15 patients presenting with residual thoracic mass

Diagnosis	No. of patients
Success	14
Hodgkin's lymphoma	4
Non-Hodgkin's lymphoma	1
Fibrosis	4
Necrotic tissue	1
Tuberculosis	2
Normal enlarged thymus	2
Failure	1

that a pancreatic injury during laparoscopic biopsy of a peripancreatic lymph node might have caused a pancreatic fistula leading to an abscess. Indeed, pancreatic tissue was found with the lymph node sample on histology.

Three patients (3 per cent) required conversion to open surgery. As mentioned above, one patient had a thoracotomy for pulmonary haemorrhage. A second required a mediastinotomy because of inefficient lung collapse that did not permit a safe thoracoscopic examination. Finally, in the laparoscopic group, a technical problem led to the need for a laparotomy. In all these three patients, a pathological diagnosis was obtained.

The mean duration of postoperative stay was 1 (range 1–2) days after mediastinoscopy, 3 (range 1–10) days after thoracoscopy and 3 (range 2–14) days after laparoscopy.

The overall success rate of surgical endoscopic procedures was 87 per cent. Twelve of 13 mediastinoscopies were successful. The patient whose mediastinoscopy was not contributory had repeat thoracoscopy 1 month later. In the thoracoscopic group, the success rate was 92 per cent. Only nine of 15 laparoscopic procedures were successful; there were three complete failures and three partial failures, due to inadequate size of the lymph node biopsies. In total, four patients had a difficult phenotyping (partial failure). In two, no further surgery was necessary; in the other two, a repeat endoscopic procedure was performed successfully. The final histopathological subtypes of the lymphomas are listed in *Table 3*. The histological details of all failed cases are presented in *Table 4* and of patients investigated for possible residual disease in *Table 5*.

Discussion

Despite the rapid development of surgical endoscopy, laparoscopy and/or thoracoscopy are not used routinely as diagnostic and staging tools in the diagnosis and management of lymphoma. In 1993, Ribet and Cardot[14] reported a series of 480 anterior mediastinal tumours. Fifty-two were lymphomas; 32 were biopsied via mediastinotomy and five via thoracotomy or sternotomy. Laparotomy, thoracotomy and sternotomy all have the inherent morbidity of major surgery. In a series of 133 laparotomies for Hodgkin's disease, Jockovitch *et al.*[15] reported a 9·8 per cent rate of small bowel obstruction, requiring repeat laparotomy in most cases.

An alternative, less invasive biopsy technique is done using ultrasonographic or computed tomography (CT) guidance. Radiologically guided biopsies were previously performed using fine-needle aspiration cytology but this gave a pathological diagnosis in only 64 per cent of patients[6]. With core-needle biopsies, the diagnostic accuracy is around 80 per cent in many recent series, especially when several samples can be obtained using a coaxial technique[1,3]. In the series of Ben-Yehada *et al.*[1] 8 per cent of the patients received therapy on the basis of the core-needle biopsy alone. In the study of Pappa *et al.*[3] the rate was similar (83 per cent). In the latter study, the size of the samples was sufficient for phenotyping in all cases. The authors point out that they did not encounter the problem of missing large follicles, a theoretical limitation of IGNB for assessment of follicularity[2].

All failures of IGNB reported in recent papers have subsequently required an open surgical biopsy[1,2]. Since 1991, the present authors have used a surgical endoscopic technique rather than open surgery whenever possible. This policy has resulted in an indisputable advantage for patients whose biopsy was successful, because of the limited incisions and the short hospital stay. The success rates of thoracoscopy (56 of 61) and mediastinoscopy (12 of 13) found in this series are similar to those of other studies dealing with these techniques for mediastinal masses and/or lymph nodes[16–18].

Few studies of laparoscopy for biopsy of lymphomas are available[7–10]. In this study, laparoscopy yielded less than thoracoscopy or mediastinoscopy. Overlooking positive lymph nodes during laparoscopy is a limitation of the method[19,20]. In a series of 55 laparoscopies performed in 52 patients with suspicion of lymphoma, Conlon *et al.*[9] reported a diagnostic accuracy of 98·2 per cent. The high failure rate in the present series may be due to the fact that most abdominal masses or lymph nodes are referred to the radiologist for percutaneous biopsy[4]. Only patients not selected for IGBN had surgery. These patients either have a small lesion which may be difficult to reach laparoscopically, especially in the obese, or a high suspicion of Hodgkin's disease or low-grade non-Hodgkin's lymphoma. In the latter situation, examination of a whole lymph node is usually essential. Dissecting and removing a whole lymph node located in the retroperitoneum is sometimes difficult. Proximity of large vessels and/or pancreas may prompt excessive caution and lead to an inadequate biopsy[2]. Experience may also matter. Recently, it was found that adapting the patient's position to the procedure was helpful in exposing the retroperitoneum, making the operation easier and safer.

Surgical endoscopic techniques are especially beneficial for ruling out residual disease when a mass is still present after therapy. Despite imaging, it may be difficult to assess whether a residual mass is malignant. Thoracoscopic and laparoscopic techniques allow for multiple biopsies in different areas of the residual mass, thus reducing the likelihood of a false-negative diagnosis.

Based on this study, the following management may be proposed. Abdominal masses or lymph nodes of sufficient size for percutaneous biopsy[21] should be approached primarily through IGNB. When Hodgkin's disease is suspected, the need to examine a complete lymph node makes surgery preferable[4,6]. Open surgery may be avoided in most cases, although increased experience with laparoscopic biopsy is necessary to improve results still further. For patients with lymph nodes of the middle mediastinum, mediastinoscopy is the procedure of choice because of its high diagnostic yield as well as its low morbidity and short postoperative stay[12,22,23]. Patients with a lung nodule or other mediastinal mass are best investigated by thoracoscopy[12,16,18]. CT-guided biopsy is indicated for masses close to the chest wall and/or in patients with respiratory failure[5].

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Abscess after appendicectomy in children: the role of conservative management

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Background Intra-abdominal abscess remains a significant cause of morbidity following appendicectomy. In children, little emphasis has been placed on the non-invasive management of this complication using antibiotic therapy alone. This study reviews the experience of a paediatric surgical department in managing abscess arising after appendicectomy.

Methods Hospital records of all children undergoing appendicectomy between January 1992 and January 1997 were reviewed retrospectively.

Results Some 1024 children underwent appendicectomy over a 5-year period. Twenty three patients (2·2 per cent) developed abscesses after appendicectomy. Non-operative management with intravenous or oral antibiotics alone was successful in 21 patients, with complete clinical and radiological resolution of the abscess. Drainage of the septic collection was performed in only two patients: by laparotomy ($n = 1$) and by the transrectal route ($n = 1$).

Conclusion Antibiotic therapy alone is an efficacious and safe first-line treatment modality in children who develop this complication. Drainage of an abscess developing after appendicectomy is rarely necessary in children.

Acute appendicitis is the commonest emergency requiring abdominal surgery in children[1]. The recommended treatment is appendicectomy, and the management of affected children is standardized in most adult general and paediatric surgical units. Appendicectomy is uniformly associated with a low morbidity and mortality rate[2]. However, there remains a small yet significant morbidity attributed to complications following surgery.

Intra-abdominal abscess is an important cause of prolonged hospital stay or readmission following appendicectomy. The accepted treatment of this complication has followed traditional surgical philosophy which requires drainage of the abscess[1,3]. To this end, there has been a trend towards the use of minimally invasive techniques such as ultrasonographically guided drainage via the percutaneous, transvaginal or transrectal routes, reserving laparotomy for cases in which the intra-abdominal collections are not amenable to evacuation by these methods[3–6]. Although most drainage techniques employ the concomitant use of broad-spectrum antibiotics, little emphasis has been made in the literature regarding solely non-invasive management of abscess after appendicectomy with antibiotic therapy alone. In this study, recent experience in the management of this complication in children is presented.

Patients and methods

The hospital records of all children undergoing appendicectomy between January 1992 and January 1997 were reviewed. Patients who developed an intra-abdominal abscess following appendicectomy were entered into the study. Children who had an established appendiceal abscess at initial presentation were excluded from further analysis. Eligible patients were identified and the following information recorded: age, sex, clinical features, white cell count, radiological diagnosis, site and size of abscess, method of definitive treatment and outcome. The following details regarding the original appendicectomy were obtained: duration and nature of symptoms before diagnosis, operative findings, cultures of peritoneal swabs, antibiotic therapy and postoperative course.

All patients received intraoperative antibiotics, with cefotaxime and metronidazole administered intravenously. Antibiotics were administered for varying periods of time after operation depending on the operative findings and clinical course of the patient (*Table 1*). If free purulent peritoneal fluid was found at operation, limited lavage was performed with warm normal saline. It is not the authors' practice to insert peritoneal drains in these patients. All wounds were closed primarily irrespective of operative findings.

Following appendicectomy, an intra-abdominal abscess was suspected if the patient developed increasing abdominal pain, ileus, diarrhoea or persistent pyrexia. After the exclusion of other causes of postoperative pyrexia, such as wound, intravenous access site, urinary tract or respiratory infection, all patients with the above symptomatology underwent ultra-

Table 1 Operative findings and antibiotic duration at initial appendicectomy in patients with subsequent abscess

Operative finding	Duration of antibiotics (h)	No. of patients
Suppurative appendicitis	24	2
Gangrenous appendicitis (excluding macroscopic perforation)	48	1
Perforated appendicitis	120	20
Total		23

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sonography of the abdomen and pelvis. Patients developing the above symptoms/signs following discharge from hospital had similar studies performed.

Criteria for the diagnosis of an intra-abdominal abscess were a defined intraperitoneal collection on ultrasonography in combination with symptoms or signs suggestive of an abscess. The presence of leucocytosis contributed to, but did not confirm, the diagnosis of intra-abdominal abscess. If an abscess was detected, patients were treated with intravenous antibiotics (cefotaxime and metronidazole). If the abscess was diagnosed while the patient was already receiving antibiotics, additional therapy, usually in the form of an aminoglycoside (gentamicin), was added to the therapeutic regimen. Ambulatory patients with mild symptoms were treated with oral antibiotics alone, usually a combination of cephradine and metronidazole.

Response to antibiotic therapy was monitored by an improvement in clinical symptoms (resolution of abdominal pain, ileus and pyrexia) and by serial ultrasonography. Drainage of the abscess by laparotomy or via a transrectal or percutaneous route was performed if the septic collection failed to show clinical or radiological signs of resolution.

Results are expressed as mean(s.d.).

Results

Some 1024 appendicectomies were performed over a 5-year period. Of these patients, 23 (2·2 per cent) developed an abscess after appendicectomy (12 boys and 11 girls). The median age at presentation was 11·7 (range 2·3–16) years. The initial operative findings are shown in Table 1. Patients developed symptoms and/or signs suggestive of an intra-abdominal abscess at varying periods after appendicectomy, ranging from 2 to 24 days, with most patients presenting between 4 and 6 days after surgery. Thirteen of the 23 children developed an abscess in the postoperative period whilst still receiving intravenous antibiotics, while ten developed symptoms at home following discharge.

Fever (temperature above 37·5°C) ($n = 18$) was the commonest presentation, either as an isolated symptom ($n = 3$) or in combination with abdominal pain ($n = 10$), vomiting ($n = 4$) or diarrhoea ($n = 6$). Five patients presented without fever. In these children, the commonest feature was abdominal pain ($n = 5$), either alone ($n = 2$) or accompanied by vomiting ($n = 2$) or diarrhoea ($n = 1$).

The white cell count was available in 15 patients who presented with symptoms of an intra-abdominal abscess. Of these, 12 patients had a leucocytosis (18·5(5·0) $\times 10^9$ per litre), while three did not (10·5(1·4) $\times 10^9$ per litre).

The diagnosis was confirmed by ultrasonography in all cases. The abscesses were most commonly located in the rectouterine or rectovesical space ($n = 16$) with the remainder in the right iliac fossa. The largest dimension of the abscess was 5·9(2·0) cm. Peritoneal fluid cultures were available in 11 cases and the commonest offending organism was *Escherichia coli* (seven of 11 cultures). Of the two patients who underwent drainage of the abscess, pus cultures grew *E. coli* in one while the other yielded no growth.

Twenty-one of the 23 patients were treated successfully with antibiotic therapy alone. Eighteen patients required intravenous antibiotics while four children responded to oral antibiotic treatment. The duration of antibiotic treatment was 7·5(2·5) days. In these children, the temperature returned to normal in a median of 4 (range 1–10) days and median hospital stay was 8·3 (range 2–30) days. One patient (hospital stay 30 days) had an abscess in the right iliac fossa which resolved with antibiotics but developed an additional complication of a sympathetic pleural effusion. The median time to ultrasonographic resolution of the intra-abdominal collection was 18·5 (range 7–60) days (*Fig. 1*).

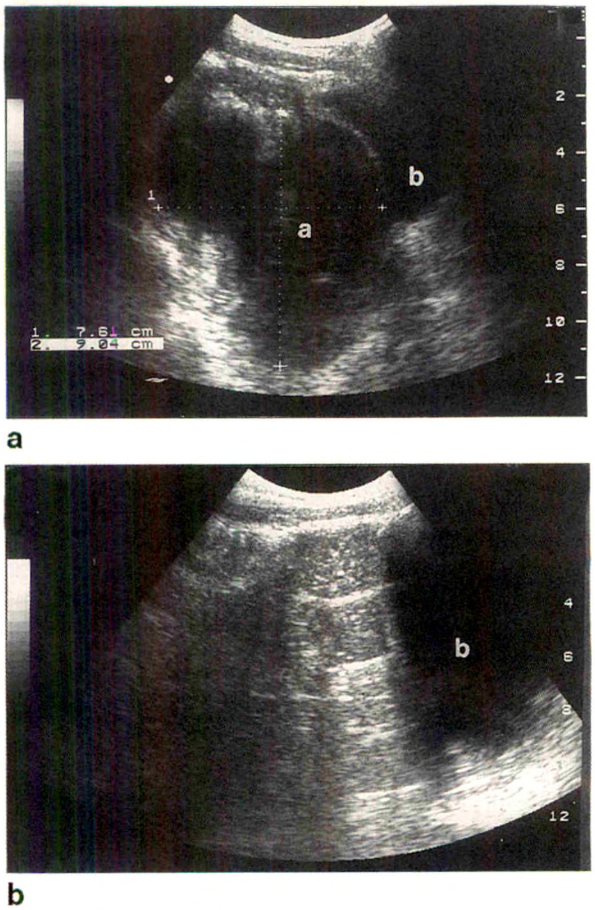

Fig. 1 **a** Ultrasonographic scan showing a large intraperitoneal abscess in the right iliac fossa. **b** Follow-up scan on the same patient showing complete resolution of the abscess after 1 week of intravenous antibiotics. a, abscess; b, urinary bladder

Non-operative treatment was not used in two patients with a pelvic abscess. One of these children underwent laparotomy and drainage as primary therapy based on the clinical condition of the child on presentation and the discretion of the attending paediatric surgeon. The other was managed successfully by ultrasonographically guided transrectal drainage. These patients were discharged 9 and 2 days respectively after drainage of the abscess.

Discussion

The routine use of prophylactic antibiotics together with improvements in the perioperative fluid management and resuscitation of children have seen a reduction in the incidence of major infectious complications following surgery for acute appendicitis[7,8]. The incidence of abscess development after appendicectomy in childhood varies from 0 to 2·2 per cent in all children with acute appendicitis[2,9,10]. The present incidence of 2·2 per cent is therefore comparable with previous reports. In children with perforated appendicitis, the reported abscess rate ranges from 0 to 6 per cent[11-13]. As expected, in the present study this complication usually followed surgery for perforated gangrenous appendicitis (20 of 23 patients). However, two patients with an inflamed appendix and one with a gangrenous appendix also developed a pelvic abscess.

The prevention of wound and/or intra-abdominal sepsis following perforated appendicitis has received a great deal of attention. Until now, the only therapeutic intervention proven to reduce the incidence of these septic complications following appendicectomy is the use of prophylactic antibiotics[8,14,15]. Peritoneal lavage with normal saline at the time of initial surgery is believed to reduce peritoneal contamination and reduce the likelihood of septic complications[7,16]. There is, however, no conclusive evidence to support the use of this procedure. The value of antibiotic lavage also remains uncertain[17,18]. The insertion of peritoneal drains at the time of operation to prevent intraperitoneal collections remains controversial and has been associated with an increase in postoperative septic complications[14,19].

In this study about half of the abscesses occurred while the patient was still receiving intravenous antibiotics. This is in agreement with an earlier report[9]. Furthermore, patients on intravenous antibiotic therapy may not manifest the classic symptoms and/or signs associated with intra-abdominal abscess. These observations enforce the need for vigilance and regular clinical monitoring in the postoperative care of these patients.

Traditional surgical doctrine dictates that pus should be drained. As a result the recommended management of the intra-abdominal abscess developing after appendicectomy is to drain or evacuate purulent collections[1-3]. Techniques for peritoneal drainage have evolved towards minimally invasive methods such as percutaneous, transrectal or transvaginal drainage under ultrasonographic or computed tomographic guidance, reserving laparotomy for instances in which these procedures are not feasible or fail[3-6]. Such procedures, although efficacious, are invasive, may require a general anaesthetic and cause significant distress and discomfort to the apprehensive child. Little emphasis exists in the literature regarding the use of antibiotic therapy alone without recourse to drainage for abscess after appendicectomy in children.

The present study has illustrated the feasibility of managing this septic complication in children largely by the sole use of antibiotics without drainage. These findings have been supported recently by a smaller study in children which reported complete resolution of the abscess in eight of ten patients with the sole use of antibiotics[9]. Notably, in the present study, intravenous antibiotics were not universally required as four patients made a satisfactory recovery on oral antibiotics alone. Neither the age nor sex of the children nor the site, size or radiological appearance of the abscess collection had any correlation with the response to non-operative therapy, demonstrating the versatility of this management policy.

In summary, this study has shown that formal drainage procedures are required only in rare circumstances in children with this postoperative complication. Treatment should be tailored to the individual patient's response with regular clinical and radiological assessment. Antibiotic therapy alone is an efficacious first-line treatment in children who develop abscess after appendicectomy.

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Influence of a defunctioning stoma on leakage rates after low colorectal anastomosis and colonic J pouch–anal anastomosis

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Background Anal sphincter function is increasingly preserved following rectal excision for cancer and provides a better quality of life for patients than does a permanent colostomy. However, anastomotic complications may cause considerable morbidity and mortality. This retrospective study examined the incidence of anastomotic complications following two forms of reconstruction after resection for mid-rectal cancer: colonic pouch–anal anastomosis (CPAA) and low colorectal anastomosis (LCRA).

Methods Some 258 consecutive patients with mid-rectal cancers between 6 and 11 cm from the anal verge underwent proctectomy with mesorectal excision and either CPAA or LCRA. The incidence of clinical and radiological leaks was determined in these patients who were considered in three groups: LCRA (defunctioning stoma), LCRA (no defunctioning stoma) and CPAA (all defunctioned).

Results In the LCRA group without a defunctioning stoma, a clinical leak occurred in 17·0 per cent, compared with two of 30 in the LCRA group with a defunctioning stoma. In the CPAA group a clinical leak occurred in 4·9 per cent of patients, which was not significantly different from the rate in those with a defunctioned LCRA. Patients with a non-defunctioned LCRA were more likely to suffer a clinical anastomotic leak ($P = 0·01$), peritonitis ($P = 0·001$) and require unscheduled reoperation ($P = 0·006$) than those with a defunctioned LCRA and/or CPAA.

Conclusion The use of a protective defunctioning stoma is advocated in conjunction with LCRAs.

Recent years have seen a dramatic decrease in the frequency of abdominoperineal resection of rectal cancers in favour of sphincter-preserving procedures. Although it is generally agreed that patient satisfaction and quality of life are superior following sphincter-preserving surgery, significant morbidity and mortality do occur, with anastomotic dehiscence being the primary concern. The incidence of anastomotic leakage following anterior resection varies from 2 to 17 per cent depending on the level of the anastomosis[1], surgical expertise[2] and the method of reconstruction[3]. In the presence of generalized abdominal sepsis, mortality rates of around 50 per cent are reported[4,5] and those surviving the immediate consequences of anastomotic failure can expect a poor functional result because of stenosis and reduced compliance of the neorectum[6]. Although oncologically sound, the benefits of mesorectal excision may be associated with a high incidence of anastomotic dehiscence[7,8] and the routine use of defunctioning stomas has been suggested for these high-risk anastomoses[4].

Three approaches to reconstruction following rectal resection are available. In low rectal cancer (less than 6 cm from the anal verge) the authors routinely use colonic pouch–anal anastomosis (CPAA)[9]. For cancers in the upper rectum, above 12 cm, the lesion is resected and the distal mesorectum transected at least 5 cm below the inferior margin of the tumour followed by a low colorectal anastomosis (LCRA). The optimum reconstruction following mesorectal excision in cancers with an inferior margin falling between 6 and 11 cm is unknown and the decision between CPAA and LCRA is left to the discretion of the surgeon. This paper reports experience of anastomotic complications in a series of 258 patients with cancers between 6 and 11 cm, treated with CPAA or LCRA.

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Patients and methods

Between July 1987 and December 1995, 398 consecutive patients underwent anterior resection for rectal cancer 12 cm or less from the anal verge. A group of 258 patients was selected with cancers situated between 6 and 11 cm from the anal verge in whom the decision to form CPAA or LCRA was made at operation. All rectal resections included the mesorectum and from 1992 total mesorectal excision (TME) with autonomic nerve preservation according to the method described by Heald and Ryall[10] was employed. In all cases the splenic flexure was mobilized and high vascular ligation was performed. Proximal descending or distal transverse colon was used for anastomosis to the rectum or anus and adequate vascularity of the colon was confirmed by identification of pulsatile blood flow on dividing a distal appendix epiploica vessel or at the marginal artery. All CPAAs were defunctioned through a loop ileostomy or colostomy but for LCRA this decision was left to the discretion of the surgeon, depending on the patient's condition, intraoperative progress and testing of the anastomosis by air insufflation. Thus, three groups were available for study: non-defunctioned LCRA, defunctioned LCRA and defunctioned CPAA.

One hundred and twenty-two patients had CPAA and 136 LCRA. The technique of CPAA has been described previously[11]. The LCRAs were either double stapled ($n = 88$) or sutured ($n = 48$); all anastomoses in the former group were tested routinely by air insufflation. In all cases, two vacuum drains were

Table 1 Characteristics of patients in the three groups

	LCRA			
	Defunctioned (*n* = 30)	Not defunctioned (*n* = 106)	CPAA (*n* = 122)	*P*§
Age (years)*	66(13)	61(13)	62(12)	0·24
Men†	14 (47)	53 (50)	73 (59·8)	0·4
Distance from anal verge (cm)*	8·37(1·59)	8·49(1·42)	7·22(1·18)	< 0·0001
Margin of clearance (cm)*	3·52(1·20)	3·42(1·06)	2·99(1·45)	0·02
Calculated level of anastomosis (cm)*	4·75(1·60)	5·05(1·70)	—‡	0·4
Dukes stage†				0·11
A	2 (7)	8 (7·5)	10 (8·2)	
B	13 (43)	52 (49·1)	68 (55·7)	
C	7 (23)	30 (28·3)	36 (29·5)	
D	8 (27)	16 (15·1)	8 (6·6)	
No. of lymph nodes examined*	15·3(8·2)	15·1(7·1)	16·6(8·8)	0·57
Preoperative radiotherapy†	2 (7)	12 (11·3)	22 (18·0)	0·1

*Values are mean(s.d.); †values in parentheses are percentages; ‡anastomosed to pectinate line in anal canal. LCRA, low colorectal anastomosis; CPAA, colonic pouch–anal anastomosis. §Analysis of variance or Fisher's exact test

placed in the pelvis to reduce perianastomotic collections. A defunctioning stoma was performed in all patients who had CPAA and in 30 patients with LCRA. The level of the anastomosis was calculated in patients with a LCRA by subtracting the distal resection margin from the tumour level as measured at preoperative proctoscopy. A subgroup of patients received preoperative radiotherapy determined by the presence of tumour fixation. All patients received standard bowel preparation and three doses of prophylactic antibiotics. The characteristics of all patients appear in *Table 1*.

All patients with a CPAA and those who had LCRA and a defunctioning stoma underwent water-soluble contrast enema before stoma closure, 8-10 weeks after operation. In addition, a water-soluble contrast enema was performed in any patient with features suggesting anastomotic leak. Clinical leak was defined as evidence of generalized or pelvic infection associated with symptoms such as abdominal pain, fever, leucocytosis or shock. The leakage was confirmed by contrast enema, imaging or at reoperation. Asymptomatic anastomotic leaks were identified at routine contrast studies before stoma closure and all were treated with retardation of stoma closure.

Statistical analysis

Values are given as mean(s.d.). Fisher's exact test was used to compare qualitative variables and analysis of variance for quantitative variables. $P<0·05$ was considered statistically significant.

Results

The postoperative course was free from complications in 61·2 per cent of patients (*Table 2*). The duration of hospital stay was significantly longer in the CPAA and defunctioned LCRA groups. The reported values include days spent in hospital for stoma closure and readmission for complications after discharge. Resection was considered palliative because of metastatic disease in eight patients in the defunctioned LCRA group, 16 patients in the non-defunctioned LCRA group and eight patients in the CPAA group.

In the LCRA group without a defunctioning stoma, clinical anastomotic leaks occurred in 18 of 106 patients and included nine patients with frank peritonitis, seven with pelvic abscess and/or five with rectovaginal fistula. Seventeen patients in this LCRA group required reoperation (*Table 3*). Clinical leakage in the subgroup of LCRA with a defunctioning stoma occurred in two patients, resulting in one case each of pelvic abscess and rectovaginal fistula, both managed operatively. Reoperation in this group was also required in one patient with early postoperative small bowel obstruction. An asymptomatic leak occurred in one patient, which healed on conservative management with delay in stoma closure. Seventeen per cent of stapled anastomoses required reoperation for clinical leak compared with 8 per cent of sutured anastomoses ($P=0·25$). The use of a

Table 2 Postoperative complications and hospital stay

	LCRA			
	Defunctioned (*n* = 30)	Not defunctioned (*n* = 106)	CPAA (*n* = 122)	*P*‡
No complications*	16 (53)	68 (65)	74 (60·7)	0·49
Anastomotic leak*				
Clinical	2 (6)	18 (17·0)	6 (4·9)	0·01
Asymptomatic	1 (3)	0 (0)	4 (3·3)	
Peritonitis*	0 (0)	9 (8·5)	0 (0)	0·001
Pelvic abscess*	1 (3)	7 (6·7)	2 (1·6)	0·14
Reoperation*	3 (10)	17 (16·0)	4 (3·3)	0·006
Mean(s.d.) hospital stay (days)†	30·3(25·5)	17·8(14·0)	23·7(13·6)	0·008

*Values in parentheses are percentages. †Hospitalization included readmission for stoma closure and complications. LCRA, low colorectal anastomosis; CPAA, colonic pouch–anal anastomosis. ‡Analysis of variance or Fisher's exact test

Table 3 Deaths and complications requiring reoperation

	LCRA		
	Defunctioned (*n* = 30)	Not defunctioned (*n* = 106)	CPAA (*n* = 122)
Death	0	2	1
Peritonitis	0	9	0
Pelvic abscess	1	5	1
Rectovaginal fistula	1	3	3
Bowel obstruction	1	0	0

LCRA, low colorectal anastomosis; CPAA, colonic pouch–anal anastomosis defunctioning stoma was similar between the stapled and sutured group: 20 *versus* 25 per cent respectively ($P = 0{\cdot}69$).

In the CPAA group clinical leaks occurred in six patients and asymptomatic leaks in four. No peritonitis occurred in this group; clinical leaks presented as fever ($n = 1$), pelvic abscess ($n = 2$) and pouch vaginal fistula ($n = 3$). Four patients required further surgery (*Table 3*); the remainder responded to conservative treatment with antibiotics and delay in stoma closure. Overall, patients with non-defunctioned LCRA were significantly more likely to suffer a clinical anastomotic leak ($P = 0{\cdot}01$) and peritonitis ($P = 0{\cdot}001$) than those with a defunctioned LCRA and CPAA, and to require unscheduled reoperation than those with CPAA ($P = 0{\cdot}006$).

Two patients in the non-defunctioned LCRA group died after operation. One patient who also underwent extended right nephrectomy for renal carcinoma died on day 7 after reoperation for peritonitis due to ischaemic infarction of the left colon. The second patient died on the sixth day after operation from fulminant septic shock despite intensive medical management and early reoperation for peritonitis due also to colonic necrosis. In the CPAA group one patient with cirrhosis who had a palliative resection died on day 31 after operation from massive variceal haemorrhage.

As a consequence of septic complications, stomas were permanent in one of 30 patients in the defunctioned LCRA group and 2·8 per cent (three of 106) in the non-defunctioned LCRA group compared with 1·63 per cent (two of 122) in the CPAA group ($P = 0{\cdot}69$). Cardiac, respiratory and thrombotic complications occurred equally in CPAA and LCRA groups whether or not a defunctioning stoma was used and are not detailed in this report.

Discussion

The introduction of TME has been a major advance in the surgical strategy for rectal cancer resulting in a reduction in local recurrence without adjuvant therapy[5,7,12], but it is often associated with a high frequency of anastomotic dehiscence[7,8]. Following TME, the distal rectum is divided leaving a variable length of rectum, aiming to maintain an adequate distal resection margin of at least 2 cm of rectal wall. Such a resection potentially endangers the blood supply to the residual distal rectum and leaves a large pelvic space for the accumulation of clot and serous fluid with concomitant risk of pelvic infection. These features almost certainly contribute to the high frequency of anastomotic problems which have been described.

A recent analysis of 219 LCRAs at a median distance of 5 cm from the anal verge[1] reported an incidence of anastomotic problems similar to that of the present study. Leaks occurred in 17·4 per cent of patients and major leaks, presenting as peritonitis or pelvic abscess, in 11 per cent. Fifty seven per cent of the anastomoses were defunctioned compared with 22·0 per cent in this series, in which an overall clinical leak rate of 14·7 per cent for LCRA was observed. Six of 62 patients (10 per cent) without a defunctioning stoma in Karanjia's series[1] developed peritonitis with three deaths compared with an incidence of 8·5 per cent with two deaths in the present patients with LCRA and no defunctioning stoma. In patients with a defunctioned LCRA, the frequency of clinical leaks was 8·2 per cent in the series cited and 7 per cent (two of 30 patients) in this report. Long-term sequelae of anastomotic sepsis led to permanent stomas in 5 per cent of the patients in Karanjia's series and 2·9 per cent of those in the present series of LCRAs. Aitken[8] described an overall clinical leak rate of 14 per cent in a smaller series of TME; however, this included cancers up to 16 cm from the anal verge and the use of defunctioning stoma was not indicated.

A lower incidence of anastomotic complications following similar surgery has been reported by other groups undertaking TME for rectal cancer[5,12]. In one study there was a 2·9 per cent incidence of clinical anastomotic leak with no deaths, but this series included patients with direct coloanal anastomoses as well as low stapled anastomoses. In another study[5], an incidence of clinical leakage of 1 per cent after anterior resection with TME was reported, but over half of the patients had tumours situated between 11 and 20 cm from the anal verge so direct comparison is not possible.

Symptomatic anastomotic complications following stapled or handsewn CPAA are reported in up to 8·6 per cent of patients with or without a defunctioning stoma[3,13–15]. Although these series are small, their rates are similar to the present reported clinical leak rate of 4·9 per cent in the CPAA group, with reoperation required in 3·3 per cent of patients. These results are similar to those for defunctioned LCRAs in this series, and indeed there is little difference between CPAA and a non-defunctioned LCRA in terms of duration of hospitalization and complications. However, it is perhaps relevant that although all cancers fell between the 6 and 11 cm margin, overall CPAA was employed in the treatment of more cancers at the lower end of this spectrum, where LCRA may be more hazardous.

There are theoretical benefits in the use of CPAA over defunctioned LCRA. In CPAA the anastomosis is not compromised by the potentially poor vascularity of the distal rectum, and the volume of the colonic pouch and its mesocolon reduces the pelvic dead spaces, which in combination with adequate suction drainage should help prevent pelvic collections. In addition, recent evidence from Doppler studies indicates that vascularization of the apex of the colonic pouch is better preserved than that of terminal colon[16] supporting the concept that this region is the preferred site for anastomosis. Furthermore, the extrapelvic position of the coloanal anastomosis allows fistulas to evacuate spontaneously via the anus, thereby minimizing spread of pelvic sepsis. The required length of rectum at which a colonic pouch offers no further functional advantage over direct colorectal anastomosis is uncertain, but when LCRA follows TME, there is unlikely to be significant reservoir function.

It is apparent that unprotected LCRA carries a considerable risk of death and morbidity from anastomotic complications and, on the basis of the present series and that of others[4], it appears prudent to employ a defunctioning stoma with all high-risk LCRAs. In terms of anastomotic complications, there is little difference between CPAA (all defunctioned) and defunctioned LCRA and ultimately the choice should be directed by long-term functional outcome when the level of the tumour permits this choice.

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Outcome after 'curative' surgery for carcinoma of the lower third of the rectum

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Background Controversy exists about the optimal surgical resection for lower third rectal carcinoma. The aim of this retrospective study was to analyse whether the type of surgery is a significant predictor of outcome after curative surgery alone.

Methods Eighty-two consecutive patients underwent abdominoperineal rectum excision (APRE, 41 patients) or sphincter-saving operation (SSO, 41 patients) for adenocarcinoma at 3·5–7·5 cm from the anal margin. Cox proportional hazards technique with univariate and corrected (multivariate) analyses and the Kaplan–Meier life-table method were used to evaluate the data.

Results Tumour wall penetration and lymph node involvement, but not the tumour level or the type of surgery, were found to be significant predictors of outcome. The local recurrence rate at 1, 2 and 5 years was 10, 22 and 26 per cent respectively after APRE, and 5, 13 and 21 per cent after SSO. The disease-free survival rate at 1, 2 and 5 years was 85, 67 and 58 per cent respectively after APRE, and 88, 78 and 62 per cent after SSO.

Conclusion Tumour-related factors are significant predictors of outcome. The type of surgery (APRE or SSO) did not seem to be a significant variable in this non-randomized study.

Controversy surrounds the optimal curative resection for carcinoma of the lower third of the rectum. Published series on the results of abdominoperineal rectum excision (APRE) and sphincter-saving operations (SSOs) in rectal carcinoma are difficult to assess. Most authors report on cancer of the whole rectum, while others have reported only on middle and lower third rectal cancers together. For an appropriate comparison of techniques, however, only a limited part of the rectum should be studied because outcome deteriorates with decreasing distance between tumour and anal verge[1,2]. It is agreed that complete mesorectal excision and a distal margin of 2 cm are adequate to contain local cancer spread[3,4]. Strict application of the 2-cm distal margin rule, however, means that every carcinoma in the lower third of the rectum has to be treated by APRE. Indeed, if one takes into account smooth muscle shortening in the fresh, unpinned specimen of about 50 per cent of its *in situ* length and a 2–4-cm length of the anal canal in the conscious patient, the lower edge of a rectal cancer would have to be located at 6–8 cm above the anal verge for an SSO to be indicated. In clinical practice, however, this theoretical rule is not always respected.

The outcome in patients with cancer in the lower third of the rectum was therefore reviewed to identify predictors of oncological outcome and, more specifically, to evaluate whether the type of operation (APRE or SSO) is related to failure, i.e. local or distant disease recurrence.

Patients and methods

Eighty-two consecutive patients with carcinoma of the lower third of the rectum were studied. The lower third of the rectum was defined as the zone extending from the anorectal ring to 7·5 cm from the anal margin[5] and all patients underwent primary 'curative' surgery (R_0) between January 1984 and December 1993. Exclusion criteria were rectal tumours extending into the anal canal (21 patients), intraoperative tumour breach or soiling (eight patients) and perioperative adjuvant (chemo)radiation (12 patients). A sphincter-saving procedure was performed in 41 patients and an APRE in another 41. Five patients had a synchronous gastrointestinal carcinoma, two in the APRE group and three in the SSO group, treated at the time of rectal surgery. Comparative analysis showed no significant difference with regard to sex ratio, tumour diameter, depth of tumour wall penetration, lymph node involvement, tumour node metastasis (TNM) stage, differentiation grade, synchronous carcinoma and operating time between the APRE and SSO groups. Mean(s.d.) age of patients in the APRE and SSO groups was 68(10) and 60(10) years respectively $P < 0·001$, *t* test). The mean(s.d.) distance from the anal margin, measured with a rigid proctoscope, was 4·5(1·2) cm in the APRE group compared with 5·3(1·1) cm in the SSO group ($P = 0·001$, *t* test). Of four surgeons, one performed 24 of the 41 SSOs ($P < 0·001$, χ^2 test).

A sphincter-saving procedure consisted of low anterior resection (11 patients), restorative rectal excision with straight coloanal anastomosis (12) or colon pouch–anal anastomosis (18). The anastomosis was hand sewn in 22 patients and stapled in the remainder. A protective stoma was constructed in 23 patients.

The mean(s.d.) duration of hospital stay was 19·7(9·5) days after APRE and 17·7(9·2) days after SSO (*P* not significant). Postoperative complications occurred in 40 patients: in 18 of 41 after APRE and in 22 of 41 after SSO (*P* not significant). Postoperative complications after APRE were wound infection (five patients), bladder dysfunction (four), ileus (three), urinary tract infection (UTI) (two), bleeding (two), pulmonary complications (two), deep venous thrombosis (one), urethral fistula (one) and colostomy retraction (one). In the SSO group symptomatic anastomotic leakage occurred in nine patients, UTI in four, ileus in four, pulmonary complications in three, wound dehiscence in one, bladder dysfunction in one and delirium in one.

Follow-up was complete up to 31 December 1995. All patients were re-examined at 6-month intervals, including serum carcino-

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embryonic antigen determination, ultrasonography of the liver and chest radiography. Colonoscopy was performed at 1 year and thereafter at 3-year intervals if normal. When a recurrence was suspected abdominal computed tomography (CT), endorectal ultrasonography (after SSO) and whole-body positron emission tomography with $[^{18}\text{F}]$fluorodeoxyglucose (since 1990) was performed. Pelvic magnetic resonance imaging and thoracic CT were performed only when suggested by the radiologist.

Time to event analyses were performed using the Cox proportional hazards technique. Individual or univariate analysis as well as corrected, multivariate analysis was performed to identify the optimally combined prognostic group of factors. The events studied were local recurrence and local or metastatic recurrent disease (disease-free survival). For each analysis the following potential prognostic variables were taken into account: age, sex, concomitant disease (yes/no), American Society of Anesthesiologists score, localization of the tumour from the anal margin, maximum tumour size, tumour differentiation grade, tumour wall penetration, lymph node involvement, TNM stage, synchronous gastrointestinal carcinoma, type of surgery (APRE or SSO), surgeon, operating time and intraoperative bleeding.

Cumulative probabilities of local recurrence or disease-free survival rates were estimated using the Kaplan–Meier life-table method. Recurrence was considered local when it was located in the pelvis, whether or not in association with distant metastatic lesions. $P \leq 0{\cdot}05$ was considered statistically significant.

Results

Individual prognostic factors significantly related to one of the events studied by univariate analysis in all 82 patients are shown in *Table 1*. Tumour wall penetration, lymph node involvement, TNM stage, tumour differentiation and intraoperative bleeding were found to be related to both events. Corrected or multivariate analyses were performed to identify the combined group of factors that best predict local recurrence or disease-free survival. Lymph node involvement was identified in both analyses, whereas tumour level or type of surgery were not selected in either of them (*Table 2*). Thus, 19 of 25 patients with lymph node involvement developed local or metastatic recurrent disease compared with 12 of 57 patients with tumour-free lymph nodes.

The incidence of local recurrence and recurrent local or distant disease was found to be comparable after APRE or SSO. The local recurrence rate at 1, 2 and 5 years was 10, 22 and 26 per cent respectively after APRE, and 5, 13 and 21 per cent after SSO. The disease-free survival rate at 1, 2 and 5 years was 85, 67 and 58 per cent respectively after APRE, and 88, 78 and 62 per cent after SSO.

Because a distal safety margin of 2 cm certainly cannot be obtained in SSO for tumours located at 3–5 cm, time to event analyses were performed in this subgroup of 55 patients. The same variables were used as for the previous analyses. Univariately significant variables were the same as for the whole group of 82 patients. Again, the type of operation was not found to be significantly related to the outcome. The following variables were found to be significant in a stepwise (multivariate) analysis (the variables are given in the order in which they were selected into the model): lymph node involvement ($P = 0{\cdot}044$), tumour wall penetration ($P = 0{\cdot}023$) and tumour differentiation ($P = 0{\cdot}03$) for local recurrence; and lymph node involvement ($P < 0{\cdot}001$), tumour wall penetration ($P = 0{\cdot}001$), synchronous gastrointestinal carcinoma ($P = 0{\cdot}002$) and concomitant disease ($P = 0{\cdot}039$) for disease-free survival. The outcomes after SSO (22 patients) and after APRE (33 patients) were comparable in this subgroup of patients. The local recurrence rate at 1, 2 and 5 years was 9, 24 and 28 per cent respectively after APRE, and 9, 18 and 23 per cent after SSO. The respective disease-free survival rates were 88, 65 and 57 per cent after APRE, and 91, 77 and 64 per cent after SSO.

Table 1 Individual or univariate analysis of factors affecting local recurrence and local or distant recurrent disease

	P	
	Local recurrence	Local or distant recurrent disease
Tumour wall penetration	0·009	< 0·001
Lymph node involvement	< 0·001	< 0·001
Intraoperative bleeding	0·027	0·03
Tumour differentiation	0·023	0·015
TNM stage	< 0·001	< 0·001

TNM, tumour node metastasis

Table 2 Corrected or multivariate stepwise analysis of factors affecting local recurrence and local or distant recurrent disease

	P	
	Local recurrence	Local or distant recurrent disease
Lymph node involvement	< 0·001	0·039
Duration of operation	0·002	
ASA score	0·031	
Tumour wall penetration		0·003
Synchronous gastrointestinal carcinoma		0·009
TNM stage		0·026

Variables are given in the order in which they were selected into the model. ASA, American Society of Anesthesiologists; TNM, tumour node metastasis

Two of eight patients who had a tumour break or soiling at the time of operation developed a local recurrence after 4 and 6 months. Tumour break was reported only in the APRE group. Twelve patients had adjuvant (chemo)-radiation, seven in the APRE and five in the SSO group. Four of them developed local recurrence with distant metastasis in two between 9 and 52 months after operation. Two others developed metastatic disease at 9 and 12 months after operation.

Discussion

The level of the tumour is still probably the most important factor influencing the type of operation in a patient with resectable low rectal cancer. It has been demonstrated that the safety margin of distal clearance can be reduced to 2 cm if taking more would jeopardize the anal sphincter. Short distal resection margins have not been significantly related to pelvic recurrence[3,4,6–8]. Of course, the distal margin, or doughnut if a stapler is used, should be tumour free as well as the lateral margins. The distal safety margin is inevitably shorter after SSO than after APRE for very low rectal cancer. For an optimal comparison of techniques, a randomized trial is required. This was not a randomized trial and a selection bias may well be present. Patients in the SSO group were younger than those in the APRE group, the tumour level was somewhat higher and one surgeon performed more restorative surgery than the others. However, the distribution of all tumour-related parameters was comparable in both APRE and SSO groups, except for the tumour level. One might argue that a bias could be introduced into the data set by virtue of the selection criteria. Therefore, the outcome of the excluded patients was analysed. Although APRE seemed to be associated with an increased risk of tumour break in this series, the final outcome of these patients did not seem to be compromised.

This study included only patients who underwent curative APRE or SSO without preoperative or postoperative (chemo)radiation for carcinoma in the lower third of the rectum. The results indicate that local tumour control as well as disease-free survival are similar after SSO and APRE. Although total mesorectal excision was performed in all patients, the local recurrence rate in this series seems fairly high, indicating and confirming the quality and limits of 'curative' surgery alone. Indeed, comparable results have been reported in other non-randomized trials comparing SSO with APRE although low and mid rectal cancer were mostly analysed together[9-13]. Local recurrence rates of 20–27 per cent have been reported even after extended lymphadenectomy for tumours at or below the peritoneal reflection[14,15]. A high local recurrence rate might be explained by a high incidence of T_3 lesions: 71 per cent (29 of 41) in the APRE and 56 per cent (23 of 41) in the SSO group.

This study confirms that tumour-related variables predict outcome. It also suggests that similar control of three-dimensional tumour and lymphatic spread can be obtained by SSO and APRE for cancer in the lower third of the rectum. Since a selection bias cannot be excluded, it should not be concluded that a SSO can safely be performed in all these patients.

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Selective management of renal gunshot wounds

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Background Gunshot wounds to the kidney have been managed traditionally by surgical exploration. Concerns over increased nephrectomy rates and unnecessary explorations have placed this method under scrutiny. Selective renal exploration based on solid clinical and radiographic criteria may be a safer alternative and deserves evaluation.

Methods The medical records of 52 consecutive patients with renal gunshot wounds, who were managed between September 1994 and August 1995 by a protocol of selective exploration, were reviewed. Renal injuries were explored only if they involved the hilum or were accompanied by signs of continued bleeding. Main outcome measures were the numbers of kidneys lost, as well as the morbidity and mortality related to the management of the renal injury.

Results Three patients died from associated injuries shortly after admission. Fifteen patients suffered complications but only two had complications directly associated with the renal injury. Thirty-two patients underwent renal exploration and 17 of them required nephrectomy for major renovascular or parenchymal trauma (grade IV and V). Renal exploration was successfully avoided in the remaining 20 patients. No kidneys were lost unnecessarily as a result of this policy.

Conclusion Mandatory exploration of all gunshot wounds to the kidney is not necessary. Injuries that produce stable peripheral haematomas do not require exploration.

Most penetrating renal injuries are treated by obligatory surgical exploration[1,2]. Although small stable perirenal haematomas after stab wounds have been managed successfully without surgical intervention[3,4], most authors agree that injuries produced by bullets should be explored routinely[5,6]. However, releasing the tamponade produced by Gerota's fascia may unnecessarily increase the nephrectomy rate[7]. Despite the fact that routine proximal control of the hilar vessels is being advocated to eliminate this risk[8], this manoeuvre is not always feasible or advisable in haemodynamically unstable patients with multiple injuries.

The risk of late complications, such as haematuria, arteriovenous fistula, scarring or renal hypertension, after conservative management, has been also cited as a reason for prompt exploration[9]. However, there is no evidence that these complications are reduced by operation; on the contrary, some authors have reported on the unreliability of immediate surgery to protect against such complications[10]. Thus, a selective approach to gunshot wounds of the kidney warrants further investigation.

This study evaluated the role of selective exploration of renal gunshot wounds and assessed the clinical and radiographic criteria of such a policy.

Patients and methods

All patients with gunshot wounds to the kidney were initially included in this study. Renal injuries were diagnosed in three ways: (1) direct inspection after opening of Gerota's fascia during surgical exploration, (2) presence of Gerota's fascia penetration with renal haematoma during abdominal (but not renal) exploration, and (3) evidence of renal injury during radiographic evaluation (intravenous pyelography (IVP), computed tomography (CT), renal arteriography).

All patients were managed by a dedicated trauma team. Resuscitation was conducted according to the Advanced Trauma Life Support protocol. Patients with gunshot wounds of the abdomen were managed selectively rather than by mandatory exploration according to previously published protocols[11].

Haematuria did not constitute an indication for urgent operation, unless accompanied by peritoneal signs, haemodynamic instability or rectal bleeding. Patients with haematuria and no other findings underwent IVP and/or abdominal CT. Patients who had haematuria and were operated on for other reasons had both perirenal areas inspected, and the presence of bilateral kidneys was confirmed by palpation. In the presence of active bleeding or expanding haematoma Gerota's fascia was opened, the kidney was mobilized, the bleeding was controlled by manual pressure and the injury was evaluated. Non-expanding but large haematomas in haemodynamically stable patients were explored after central control of the renal hilum. The management of the remaining perirenal haematomas consisted of exploration of the renal hilum and proximal ureter without breaching Gerota's fascia.

Demographic data and information regarding the injury, diagnostic tests, therapeutic procedures and outcome were recorded prospectively. Renal injuries were graded according to the recommendations of the Organ Injury Scaling Committee of the American Association for the Surgery of Trauma[12]. Statistical comparisons were conducted by using the χ^2 test and Fisher's exact test.

Results

From September 1994 to August 1995, 452 patients with non-tangential gunshot wounds to the abdomen and back were admitted. Of these 54 had renal injuries. There were 50 men and four women with a mean age of 26·2 (range

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16–50) years. The mean Injury Severity Score (ISS) was 20 (range 4–51). Associated intra-abdominal injuries were found in 48 patients, with the liver being the most commonly injured organ. Two patients died on the operating table before any assessment of their renal injuries was made and were excluded from any further analysis. Three more patients died within the first 24 h from associated injuries. No additional deaths occurred. Complications occurred in 15 patients but were associated with the renal injury in only two cases (*Table 1*). The incidence of complications among patients with nephrectomy and patients with renal repair was similar (eight *versus* five). The mean hospital stay was 16·2 (range 1–91) days.

Fig. 1 shows the treatment of the 52 patients. The type of management with regard to the grade of renal injury is shown in *Table 2*.

Patients with no laparotomy

All four patients treated non-operatively demonstrated gross haematuria but were haemodynamically stable and had no abdominal tenderness. They were monitored radiographically and in the absence of any complications were discharged voiding clear urine (*Table 3*).

Patients who had laparotomy without kidney exploration

In 16 patients renal exploration was avoided. Gross haematuria was detected in 11 patients, microscopic haematuria in two and no haematuria in three. Nine patients had preoperative investigation of the kidneys: eight by means of one-shot IVP and one by abdominal CT. The one-shot IVP showed no abnormality in six instances, decreased visualization of one kidney in one patient and suspected extravasation in the other. In the two latter patients a small lateral renal haematoma with no evidence of active extravasation was found. Abdominal CT demonstrated a grade III laceration of the upper right kidney without extravasation of contrast in a patient who also suffered significant liver trauma. This patient subsequently underwent surgery for bleeding from the hepatic wound, and underwent suture of this liver laceration and right hepatic artery ligation. The renal haematoma was not explored, and a repeat CT scan 1 month later demonstrated almost complete recovery of the right kidney.

Drainage of the injured area was performed in eight patients. No urine leaks were detected. All patients with haematuria demonstrated clear urine by the second day after operation.

One renal complication was identified in a patient who developed haematuria 1 month after the injury. CT re-

Table 1 Complications among 52 patients with gunshot wounds to the kidney

Patient no.	ISS	Management	Complication	Hospital stay (days)
1	16	Nephrectomy	Pneumonia, fungal sepsis	69
2	26	Renal repair	Pneumonia	37
3	14	Renal repair	Pneumonia	17
4	26	Renal repair	Pneumonia, ARDS, sepsis	65
5	20	No renal exploration	Pneumonia, ARDS, fungal sepsis	66
6	29	Nephrectomy	ARDS, sepsis	50
7	34	Nephrectomy	Multiple organ failure	91
8	16	Nephrectomy	Pancreatic fistula	43
9	20	Nephrectomy	Pancreatic abscess	15
10	26	Nephrectomy	Biliary leak	9
11	18	Renal repair	Wound infection	6
12	35	Nephrectomy	Wound infection, intra-abdominal abscess	23
13	18	Nephrectomy	Persistent pneumothorax	14
14	34	Renal repair	Urinary leak	11
15	16	No renal exploration	Late haematuria	13

ISS, Injury Severity Score; ARDS, adult respiratory distress syndrome

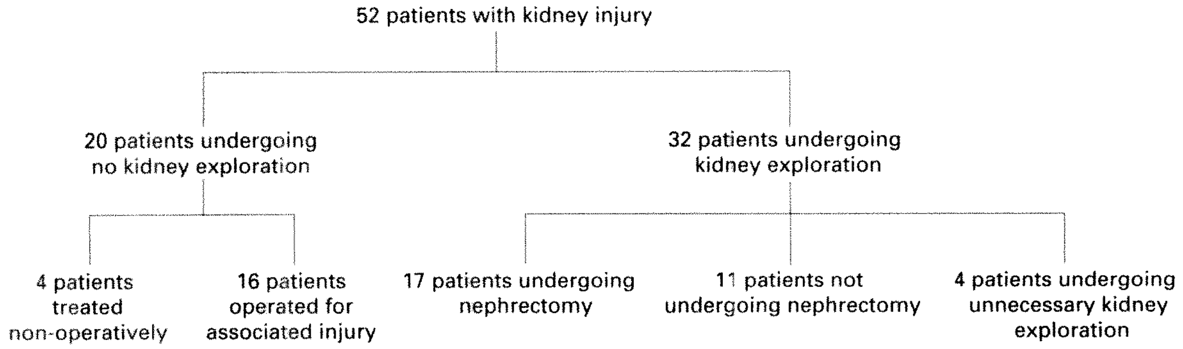
52 patients with kidney injury
20 patients undergoing no kidney exploration
32 patients undergoing kidney exploration
4 patients treated non-operatively
16 patients operated for associated injury
17 patients undergoing nephrectomy
11 patients not undergoing nephrectomy
4 patients undergoing unnecessary kidney exploration

Fig. 1 Treatment of 52 patients with gunshot wounds to the kidney

Table 2 Management according to grade of renal injury in 37 of 52 patients with gunshot wounds to the kidney

	Grade of renal injury				
	I	II	III	IV	V
Nephrectomy ($n = 17$)			1	10	6
Reconstruction ($n = 11$)		1	6	4	
Unnecessary kidney exploration ($n = 4$)	2	2			
No kidney exploration despite laparotomy ($n = 16$)*			1		
No laparotomy ($n = 4$)†		3	1		

*Only one patient was studied by computed tomography (CT); †graded according to radiographic findings on CT and intravenous pyelography

vealed lack of upper pole perfusion on the injured side. The patient underwent a successful partial nephrectomy and was discharged 7 days later with no further problems.

Patients undergoing laparotomy and kidney exploration

There were 32 patients in whom Gerota's fascia was opened.

Unnecessary explorations. In four patients exploration was conducted in violation of the protocol, as macroscopic (one patient) or microscopic (three patients) haematuria associated with small non-expanding perirenal haematomas was the sole indication for kidney dissection. Two patients had undergone a normal one-shot intravenous pyelogram before operation. Despite the presence of significant other intra-abdominal organ injuries, the kidneys were noted to have only superficial lacerations or contusions that did not require any kind of intervention.

Renal reconstructions. In 11 patients renal salvage was possible. Eight patients presented with macroscopic and three with microscopic haematuria. In six of them one-shot IVP was performed before operation but failed to show any abnormality. Partial nephrectomy was performed in four patients, debridement and suture ligation in three, packing with omentum or gelatin sponge of central holes in two, repair of the renal pelvis in one and repair of the renal vein with kidney debridement in one. One patient had a urine leak that stopped spontaneously after 12 days.

Nephrectomies. In 17 patients sacrifice of the kidney was deemed necessary. All but one of the injuries were classified as grade IV or V. Gross haematuria was present in all patients before operation. Six underwent one-shot IVP and two demonstrated poor imaging of the affected kidney. Patients who underwent nephrectomy were more often haemodynamically unstable, had more severe kidney injuries and had a higher ISS than patients who had renal reconstruction (*Table 4*).

Table 4 Comparison between patients requiring nephrectomy and patients who had renal repair after sustaining gunshot wounds to the kidney

	Patients with nephrectomy ($n = 17$)	Patients with renal repair ($n = 11$)
Mean admission SBP (mmHg)	111	122
Mean ISS	20	19
Mean admission Ht	33	34
No. of patients with $\text{SBP} < 90$ mmHg	5	2*
No. of patients with $\text{ISS} > 20$	12	4*
No. of patients with $\text{Ht} < 30$	5	1*
No. of patients with grade IV or V renal injuries	16	4*
Mean hospital stay (days)	18	16

SBP, systolic blood pressure; Ht, haematocrit; ISS, Injury Severity Score. $^*P < 0{\cdot}05$ *versus* patients with nephrectomy (*t* test)

Discussion

Although surgical exploration has been suggested as the safest way to manage renal gunshot wounds[5], there is concern that a policy of routine exploration of all injured kidneys may result in an increased rate of nephrectomy, non-therapeutic exploration and unnecessary operative delay[4,7].

A more selective approach to renal injuries could be justified, if nephrectomy and kidney-related complication rates compared favourably to results reported after routine exploration. In this study directed patient management was based on the location and the magnitude of the renal injury. Patients with active bleeding or large haematomas were explored, whereas stable haematomas away from the hilum were left undisturbed. In cases of renal exploration, proximal vascular control was practised only in the presence of central injuries, provided that the patient was haemodynamically stable. With peripheral injuries or unstable patients the kidney was rapidly delivered to the surface and haemostasis was achieved by manual compression.

This policy resulted in 38 per cent of patients avoiding unnecessary renal exploration. There was only one late

Table 3 Findings in four patients with renal gunshot wounds who were treated non-operatively

Patient no.	Site of gunshot wound	Radiographic test	Hospital stay
1	Right upper quadrant	CT: grade II kidney laceration	6 h*
2	Right lateral abdomen	CT: grade II kidney laceration IVP: normal functioning kidney, no extravasation	1 day*
3	Left flank	CT: grade III liver laceration and grade III kidney laceration (inferior pole) IVP: normal functioning kidneys, no extravasation	2 days
4	Right flank	CT: grade II kidney laceration IVP: normal function, no extravasation	2 days

*Left against medical advice. CT, computed tomography; IVP, intravenous pyelography kidney-related complication in this group (late haematuria), which was repaired with no further sequelae for the patient. The nephrectomy rate in this series was 33 per cent, which is in accordance with the literature[5,13,14].

McAninch *et al.*[8] reported nephrectomy rates of as low as 13·8 per cent but nephrectomies were deemed necessary in 25 per cent of the more seriously injured kidneys. The present authors also performed nephrectomies almost exclusively for grade IV and V renal injuries. Unfortunately, a direct comparison between the two series is not feasible because of differences in study design and renal injury classification systems.

Preoperative one-shot intravenous pyelograms do not provide useful information other than the existence of two functioning kidneys. Of 23 studies performed (22 IVPs and one CT), there were two false-positive and ten false-negative tests. Routine one-shot IVP may produce unnecessary delays or misleading results. However, this test may be useful whenever there is reasonable doubt about the presence of a contralateral kidney (e.g. previously injured victim) and intraoperative palpation may be difficult (adhesions etc.). It should be always kept in mind that this test can be easily performed on the operating table, if deemed necessary.

Patients with haematuria who are treated non-operatively should undergo radiological imaging of the kidneys. Abdominal CT with intravenous contrast can provide valuable information on perfusion, parenchymal damage and other organs. The routine combination of IVP, CT and renal angiography for accurate injury grading, as proposed by some authors, is probably excessive from an economic standpoint[2,15].

Long-term follow-up in trauma patients is notoriously difficult and is the major limitation of this study. Only three patients with renal injuries returned to the hospital within a month to undergo further imaging tests (CT in two patients and IVP in one). In all cases improvement of the renal lesion was noticed. Twelve more were followed up by clinical examination for a mean of 14 (7–32) days after the injury. No kidney-related problems were reported by these patients. Given the problems with follow-up in this population, it is prudent to consider some type of radiographic renal evaluation before discharging patients who did not undergo renal exploration, so that adequate renal function can be ascertained.

In conclusion, this study shows that gunshot wounds to the kidney do not require mandatory exploration. Selective management, based on clinical, radiographic or intraoperative findings, is safe.

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Clinical significance of clonality in thyroid nodules

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Background Many different neoplastic and hyperplastic thyroid diseases present with clinically apparent thyroid nodules. Clonality analysis indicates whether a nodule arises from the polyclonal proliferation of a group of cells or forms a clone from a genetically altered cell and thus provides objective information on the origin of the thyroid nodules. Clonality was studied in thyroid nodules using the polymerase chain reaction (PCR) assay in the X-linked human androgen receptor (HUMARA) gene by random X chromosome inactivation in women.

Methods DNA samples were obtained from 28 nodules in 21 women. All nodules and non-tumour thyroid tissues were fractioned selectively under a cryostat. Genomic DNA was isolated and digested with *Hha*I. PCR amplification of the HUMARA locus was performed using PCR mixtures containing [α-^{32}P]2′-deoxycytidine 5′-triphosphate. The PCR products were analysed by denaturing gel electrophoresis.

Results The HUMARA alleles were heterogenous in 18 of 21 patients. Among the 23 nodules from 18 patients, all of the eight papillary thyroid carcinomas were monoclonal. Two solitary nodules from follicular adenomas were monoclonal. Of the 13 follicular nodules from nodular goitres, ten were polyclonal and three were monoclonal. The monoclonal follicular nodules were larger in size (3·5 *versus* 2·0 cm, $P < 0.05$) and had a tendency towards more cystic changes than polyclonal nodules.

Conclusion PCR-based clonality study of thyroid nodules may help to distinguish hyperplastic from neoplastic nodules.

Nodules of the thyroid gland, both single and multiple, are common[1–5]. There is still no firm consensus on the best management of these lesions owing to the lack of adequate preoperative diagnostic techniques and pathological criteria to differentiate hyperplastic from neoplastic lesions[6–8].

Analysis of clonality in thyroid nodules would give important information on the origin of these lesions. Clonality analysis of thyroid nodules using differences in methylation of DNA in the active and inactive X chromosome demonstrated previously that most of the malignant nodules and some benign thyroid nodules were monoclonal[9–13]. However, several problems have prevented the application of these findings in a routine clinical setting. The Southern blot hybridization technique requires at least two restriction enzymes and relatively large quantities of DNA. Recently, a highly polymorphic short tandem repeat (STR) in the human androgen receptor (HUMARA) gene in the X chromosome was identified[14] and polymerase chain reaction (PCR) for non-random X chromosome inactivation using this gene was performed successfully to identify the clonality in various types of tumours[15,16]. DNA from 28 thyroid nodules was therefore subjected to PCR-based clonality assessment by using the size differences of the STR in the HUMARA allele; clonality was related to clinicopathological findings.

Patients and methods

Patients and tissue preparation

Twenty-eight thyroid nodules from 21 women who had undergone surgery for nodular thyroid disease were studied. These patients were identified prospectively and consecutively from April to June 1996 for a clonality study of thyroid nodules. Information from the notes was obtained to determine the demographics, nodule size and number. Patients ranged in age from 22 to 65 (mean 41) years and had from one to three clinically apparent nodules. Of the 28 nodules, 16 were nodular goitres, four were follicular adenomas and eight were papillary carcinomas. The central portion of each nodule was carefully dissected out and the tissue was snap-frozen in liquid nitrogen. A portion of the grossly non-tumorous thyroid tissue was sampled separately.

DNA extraction

DNA was extracted from the frozen tissue. In each tumour, the most homogeneous area with tumour cells was selected to reduce contamination by non-neoplastic inflammatory and stromal cells. The desired area of the tissue was fractionated by use of the cryostat fractionation technique[17] and digested overnight at 58°C in a buffer containing Tris 0·5 mol/l pH 8·9, ethylenediamine tetra-acetic acid (EDTA) 20 mmol/l, sodium chloride 10 mol/l, proteinase K 500 μg/ml and 1 per cent sodium dodecyl sulphate. After digestion, DNA was extracted with an equal volume of phenol/chloroform. DNA was precipitated with ethanol and resuspended at a final concentration of 10 μg/ml in a buffer containing Tris 3 mmol/l pH 7·5 and EDTA 0·3 mmol/l.

DNA digestion

A total of 2 μg of each DNA sample was digested with 5 units *Hha*I for 5 h at 37°C, and the reaction was terminated by incubating the mixture for 20 min at 65°C. DNA was then extracted with an equal volume of phenol/chloroform and precipitated with ethanol. DNA was washed with 70 per cent ethanol and resuspended in 20 μl water. An undigested aliquot of each DNA sample was retained as a control.

Polymerase chain reaction and gel electrophoresis

Oligonucleotide primers for the amplification of the HUMARA allele were made as described by Mutter *et al.*[15]. These primers

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were designed to amplify variable numbers of trinucleotide repeat elements and several *Hha*I sites known to be methylated on the inactive, but not on the active, X chromosome[14]. The X chromosome inactivation patterns were determined by comparison of PCR products from *Hha*I-digested and undigested DNAs isolated from thyroid nodules and matched normal thyroid tissues. Amplification was performed in a 20-μl PCR mixture (Tris 10 mol/l pH 8·4, potassium chloride 50 mmol/l, oligonucleotide primer 0·3 μmol/l each, 2′-deadenosine 5′-triphosphate 0·2 mmol/l, 2′-deoxyguanosine 5′-triphosphate 0·2 mmol/l, 2′-deoxythymidine 5′-triphosphate 0·2 mmol/l, 2′-deoxycytidine 5′-triphosphate (dCTP) 5 μmol/l containing 1 μCi [α-^{32}]dCTP (NEN DuPont, Boston, Massachusetts, USA, 3000 Ci/mmol). Thermal cycling was followed as described by Mutter *et*

Table 1 Clinical and pathological characteristics of 23 thyroid nodules

Patient no.	Age (years)	Pathological diagnosis	Gross feature	Type of follicle	Size of nodule (cm)	Clonality
1	26	Papillary carcinoma	Solid	No	1·5	Monoclonal
2	22	Papillary carcinoma	Solid	No	2·5	Monoclonal
3	49	Papillary carcinoma	Solid	No	2·5	Monoclonal
4	65	Papillary carcinoma	Solid	No	3·0	Monoclonal
5	25	Papillary carcinoma	Solid	No	2·3	Monoclonal
6	53	Papillary carcinoma	Solid	No	1·0	Monoclonal
7	49	Papillary carcinoma	Solid	No	1·5	Monoclonal
		Nodular goitre	Solid	Micro and macro	1·5	Polyclonal
8	48	Papillary carcinoma	Solid	No	0·5	Monoclonal
		Nodular goitre	Solid	Normal	1·2	Polyclonal
9	37	Nodular goitre	Solid	Micro	3·0	Polyclonal
10	42	Nodular goitre	Solid	Micro	2·0	Polyclonal
		Nodular goitre	Solid	Normal	1·5	Polyclonal
11	32	Nodular goitre	Solid	Micro and macro	2·5	Polyclonal
12	31	Nodular goitre	Solid	Normal	1·2	Polyclonal
13	36	Nodular goitre	Cystic	Normal	2·2	Polyclonal
14	61	Nodular goitre	Cystic	Macro	2·5	Polyclonal
15	38	Nodular goitre	Cystic	Micro and macro	3·5	Monoclonal
16	52	Nodular goitre	Solid	Micro and macro	4·0	Monoclonal
		Nodular goitre	Solid	Micro and macro	3·0	Monoclonal
		Nodular goitre	Solid	Micro and macro	2·5	Polyclonal
17	39	Follicular adenoma	Cystic	Micro	3·0	Monoclonal
18	44	Follicular adenoma	Solid	Micro and macro	6·0	Monoclonal

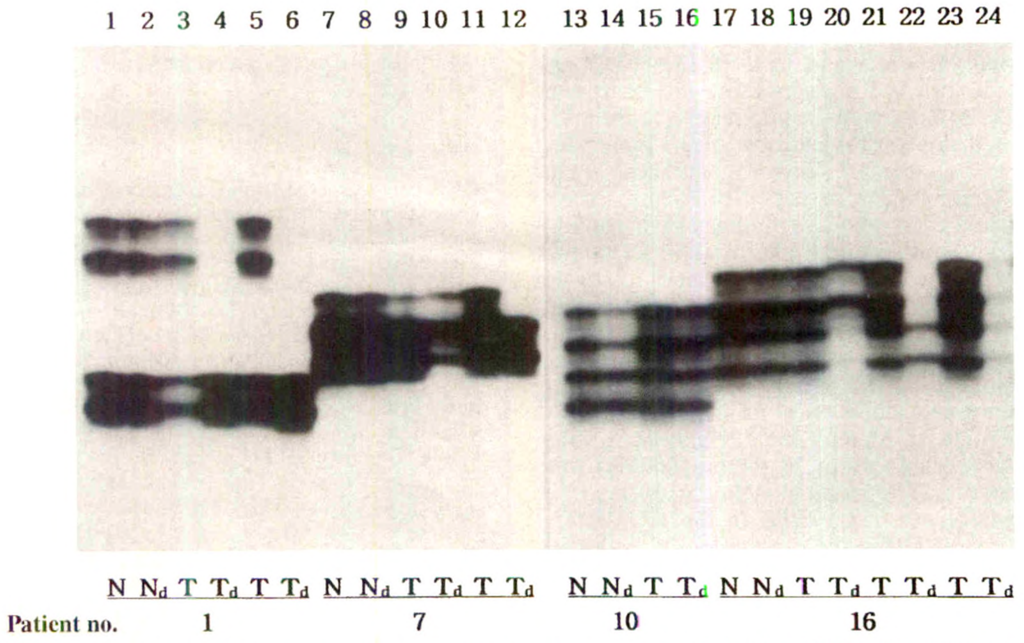
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
N N_d T T_d T T_d N N_d T T_d T T_d N N_d T T_d N N_d T T_d T T_d T T_d
Patient no.
1
7
10
16

Fig. 1 Examples of clonality analysis of thyroid nodules determined by polymerase chain reaction (PCR). The pattern of X chromosome inactivation by PCR amplification of the human androgen receptor (HUMARA) locus. X chromosome inactivation ratios were determined by comparing the amplified undigested or digested DNAs from normal thyroid (N, undigested DNA; Nd, *Hha*I-digested DNA) and tumour nodules (T, undigested DNA from tumour; Td, *Hha*I-digested DNA from tumour). In two papillary carcinomas (patients 1 and 7) one of the two HUMARA alleles was selectively eliminated (lanes 4, 6 and 12). In the adenomatous nodules of patient 7 (lanes 9 and 10) no elimination of HUMARA alleles was noted. Two nodular goitres (patients 10 and 16) showed polyclonality (lanes 16 and 24) or monoclonality (lanes 20 and 22) of different nodules. In the nodules of patient 16, different HUMARA alleles were eliminated in different nodules

al.[15] with minor modifications: (1) the reaction mixture was preheated at 97°C for 5 min; (2) incubation for 10 min at 85°C, during which 1·25 units Taq polymerase (GIBCO-BRL, Grand Island, New York, USA) were added to each reaction; (3) 25 cycles with prolonged denaturation consisting of 95°C for 1 min, 55°C for 45 s and 72°C for 90 s; and (4) final extension at 72°C for 5 min. After final extension, an equal volume of stop buffer (95 per cent formamide, sodium hydroxide 20 mmol/l and 0·05 per cent bromophenol blue and xylene cyanol) was added and the samples were loaded on to 7 per cent denaturing polyacrylamide gels containing urea 5·6 mol/l.

Statistical analysis

The clinical and pathological variables were cross-tabulated with the sources (monoclonal thyroid nodules and polyclonal thyroid nodules), and significance of association was determined using a χ^2 test and a non-parametric Mann–Whitney *U* test.

Results

Heterogeneity rates of the HUMARA allele

Of the 21 patients, 18 showed polymorphism at the STR of the HUMARA gene. Of the total 23 thyroid nodules from 18 patients, 13 were nodular goitres, eight were papillary carcinomas and two were follicular adenomas. A summary of data characterizing the thyroid nodules is given in *Table 1*.

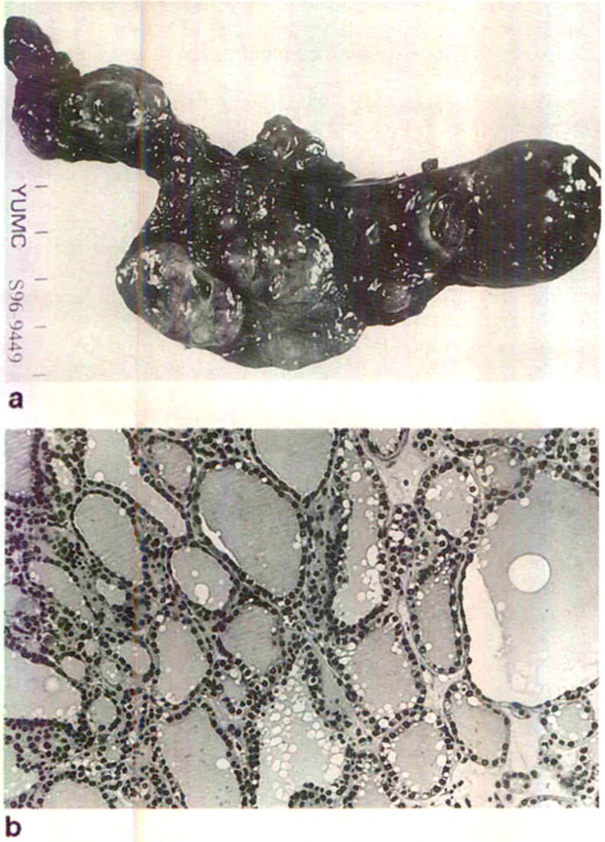

Fig. 2 **a** Gross features of a nodular goitre in patient 16. On cut section, multiple nodules were present. In the clonality assay, two nodules (right and middle) were monoclonal and the other nodule at the left was polyclonal. **b** Histopathologically, all three nodules were composed of microfollicles and macrofollicles. (Haematoxylin and eosin stain; original magnification × 100)

Clonality of the thyroid nodules

In papillary carcinomas, all of the eight nodules were monoclonal (*Fig. 1*). The two follicular adenomas were monoclonal. Of the 13 nodules from nodular goitre, ten were polyclonal and three were monoclonal. Two of the monoclonal nodules from a nodular goitre were present as separate nodules in the same patient. The X chromosome inactivation pattern of the two monoclonal nodules was different, indicating that the nodules were derived from different stem cells. The other nodule in this patient was polyclonal (*Figs 1* and *2*).

Comparison of monoclonal and polyclonal follicular thyroid nodules

Because all papillary carcinomas and follicular adenomas were monoclonal, the histological features of three monoclonal benign follicular nodules were compared with those of ten polyclonal benign follicular nodules. Monoclonal follicular nodules differed from polyclonal follicular nodules in that the monoclonal nodules were usually larger (mean 3·5 *versus* 2·0 cm, $P < 0{\cdot}05$) and had more cystic change (33·3 *versus* 20·0 per cent, $P > 0{\cdot}05$). Histologically, all of the monoclonal follicular nodules contained microfollicles; four had mixed microfollicles and normal or macrofollicles within the same lesion. In polyclonal follicular nodules, five lesions contained microfollicles.

Discussion

This study evaluated the clonality of thyroid nodules by using a PCR assay for non-random X chromosome inactivation. The HUMARA allele showed polymorphism in a high proportion of the patients with thyroid nodules and that clonality could be analysed successfully by this method. It was confirmed that malignant nodules are monoclonal and some nodules in nodular goitre are monoclonal.

It is widely accepted that tumours are monoclonal in origin[18]. Clonality analysis distinguishes monoclonal tumour nodules (nodules arising from a genetically-altered single cell and its descendants) from polyclonal hyperplastic nodules (nodules arising from the polyclonal proliferation of a group of cells)[12,19–20]. The PCR assay for non-random X chromosome inactivation has the advantage of using a small amount of genomic DNA. However, the possible disadvantage of this method is that a small amount of non-neoplastic cell contamination could provide confusing results. Studies to minimize non-neoplastic cell contamination are essential to avoid confusion or incorrect interpretation. The cryostat fractionation technique[17] seems to help in avoiding non-neoplastic cell contamination. It is also suspected that modification of PCR conditions by increasing the amount of genomic DNA and reducing the amplification cycles played a role in avoiding incorrect interpretations.

The preoperative clonality analysis of thyroid nodules using fine-needle aspiration biopsy material might provide valuable information for the clinical management of thyroid nodules. The PCR-based clonality analysis method used in this study is appropriate for the analysis of materials obtained by fine-needle aspiration biopsy because the sample is usually small. In this analysis, minimization of leucocyte contamination is essential because a large amount of blood can contaminate the biopsied samples. Recently developed microdissection and DNA extraction methods may be helpful in avoiding non-neoplastic cell contamination[21–23].

If clonality analysis using samples obtained by fine-needle aspiration biopsy could distinguish between neoplastic nodules and hyperplastic nodules before operation, the need for surgery in the management of thyroid nodules will be clearer and unnecessary operations could be avoided in patients with hyperplastic nodules.

Thyroid nodules from nodular goitre have been regarded as polyclonal, based on morphological, functional and biochemical properties[7,24–26]. However, a large proportion (33–73 per cent) of the nodules from the nodular goitre were reported as monoclonal[9–10,13,27]. These monoclonal thyroid nodules from nodular goitre present problems for pathological diagnosis because there are no objective histomorphological characteristics distinguishing monoclonal and polyclonal nodules[13,27]. Monoclonal nodules may be *de novo* neoplastic lesions or neoplasm arising in multinodular goitres. They are important because they are partially or completely unencapsulated, but further studies are needed to clarify their clinical significance. This study demonstrated that three of 13 nodules from nodular goitres were monoclonal, but the incidence was not as high as previously reported[9–10,13,27]. A study of monoclonal nodules in one patient with a nodular goitre also demonstrated that the two monoclonal nodules were formed from different progenitor cells. The clonal heterogeneity of multiple monoclonal thyroid nodules indicates that the molecular genetic events in thyroid tumorigenesis may occur in several different cells simultaneously.

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Measurement of parathyroid hormone in patients with primary hyperparathyroidism undergoing first and reoperative surgery

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Background The distinction between solitary parathyroid adenoma and hyperplasia can sometimes be difficult during surgery for primary hyperparathyroidism (pHPT), especially in patients who have undergone previous thyroid or parathyroid surgery. The use of intraoperative parathyroid hormone (PTH) monitoring as a possible diagnostic tool was therefore investigated.

Methods Intraoperative levels of PTH were measured in 119 patients during 121 operations (including 14 reoperations) for pHPT. The mean(s.d.) preoperative serum calcium level was 2·79(0·21) mmol/l. Blood samples were drawn before, and at 5 and 15 min after, excision of the first enlarged parathyroid gland. PTH was analysed electively in 61 patients and on-line by a modified assay for intact PTH in 48 patients. Both procedures were used in ten patients.

Results The mean(s.d.) decline in PTH concentration in 101 patients with primary exploration due to solitary adenoma was 63(17) per cent after 5 min ($n = 84$) and 83(10) per cent after 15 min. The patients with primary exploration because of multiglandular disease ($n = 6$) were correctly predicted not to have parathyroid adenoma.

Conclusion Measurement of PTH levels during surgery for pHPT is a highly sensitive method for differentiating between single and multiple gland disease. The on-line monitoring of PTH is clinically useful in patients who have undergone previous neck surgery. Its role in pHPT surgery at primary exploration should be evaluated in prospective trials.

Although surgery for primary hyperparathyroidism (pHPT) is successful in over 90 per cent of the patients[1–6], the intraoperative differential diagnosis between solitary parathyroid adenoma and hyperplasia can sometimes be difficult. In patients with previous thyroid or parathyroid surgery, the dissection should be kept to a minimum to decrease morbidity, yet render the patient normocalcaemic. A high frequency of multiglandular disease has, however, been demonstrated in patients with persistent or recurrent pHPT[7–9].

The use of intraoperative parathyroid hormone (PTH) monitoring as a possible tool to limit surgical trauma was therefore investigated.

Patients and methods

Patients

Some 119 patients operated on for sporadic pHPT were studied. There were 33 men and 86 women. The median age of the patients was 64 (range 26–88) years. The mean(s.d.) preoperative serum calcium level was 2·79(0·21) mmol/l. The mean(s.d.) preoperative serum level of intact PTH was 13(19) pmol/l. Twelve patients had slightly increased serum levels of creatinine. Seven patients had previously undergone thyroid surgery. Seven patients had persistent or recurrent pHPT. In three of these patients, one enlarged parathyroid gland, interpreted during operation as a solitary parathyroid adenoma, had been excised. Four of the patients had previously had a negative neck exploration. All patients with previous neck surgery underwent preoperative localization procedures.

Surgery

All patients were explored according to the principles of unilateral neck exploration[10]. Briefly, if the adenoma was found on the first explored side, it was excised together with the ipsilateral parathyroid gland and sent for frozen-section analysis. If the adenoma was not found on the first explored side, or the frozen-section analysis and/or intraoperative serum levels of PTH were inconclusive (see below), comprehensive bilateral exploration was performed. In patients with previous neck surgery, exploration was stopped after the first enlarged parathyroid gland was found. The wound was closed, but the patient kept under anaesthesia until the results from the frozen-section analysis and/or intraoperative serum levels of PTH were available.

Blood samples for parathyroid hormone analysis

Blood samples for PTH measurement were drawn from a peripheral vein immediately before, and 5 and 15 min after, excision of the first enlarged parathyroid gland. PTH was analysed electively in the initial 61 patients and on-line by a modified assay for intact PTH in 48 patients. In ten patients both procedures were used.

Adenoma diagnosis

The histological diagnosis of a parathyroid adenoma was made by the finding of one enlarged gland during neck exploration with histological features of adenoma (i.e. a rim of normal parathyroid tissue, chief cells with nuclear pleomorphism and decreased cytoplasmic fat content) and in most patients also by the sign of suppression in a normal-sized gland (chief cells with increased cytoplasmic fat)[11].

Since the half-life of intact PTH has been shown to be less than 5 min[12], a biochemical diagnosis of solitary parathyroid adenoma was made if serum levels of intact PTH decreased by more than 50 per cent 5 min after excision of the first enlarged parathyroid gland. The biochemical diagnosis of a parathyroid

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adenoma 15 min after gland excision was made when the PTH level decreased by at least 60 per cent as described previously[13].

Biochemical analysis

Serum levels of intact PTH were measured using the N-tact PTH assay (Incstar, Stillwater, Minnesota, USA). In this assay, two polyclonal antibodies were used. One antibody was a ^{125}I-labelled goat antibody directed to PTH_{1-34}. The other antibody was a goat antibody directed to PTH_{39-84}, which was bound to a solid phase. The sensitivity of this assay is 0·13 pmol/l and the within-assay variation of between 0·8 and 10 pmol/l is less than 4 per cent. The reference range in a normal population is 1·0–5·0 pmol/l.

To shorten the time for analysis, the assay was modified as described previously[14]. The time for incubation could thereby be reduced to 20 min, giving an interval between sampling and the assay result being available of about 30 min. The within-assay variation of between 0·8 and 10 pmol/l is less than 8 per cent for the rapid method. The correlation between the methods is 0·99.

Serum levels of calcium and creatinine were measured with an autoanalyser (Kodak Ektachem 700 × R-C; Johnson and Johnson, New York, USA).

Statistical analysis

The results are expressed as mean(s.d.) if not stated otherwise. Correlation between biochemical variables was assessed by linear regression analysis. A probability level for random difference of $P < 0.05$ was considered significant.

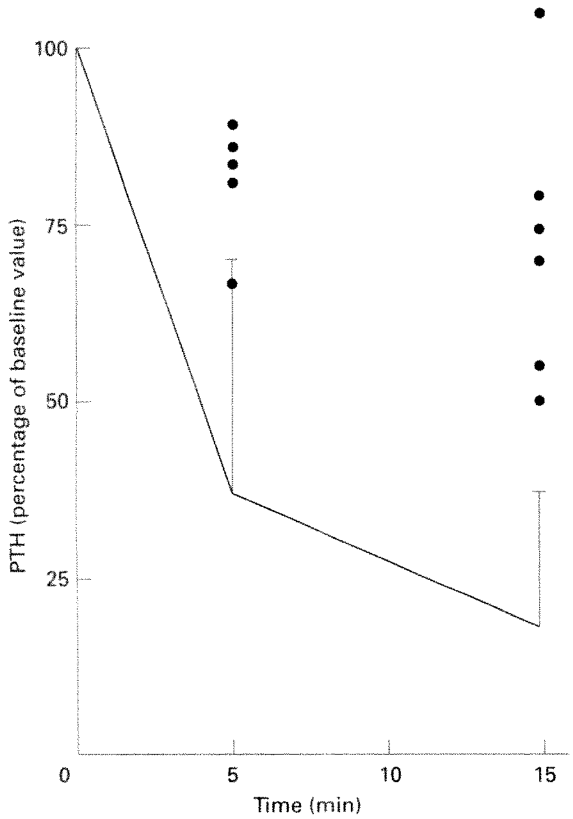

Fig. 1 Intraoperative levels of intact parathyroid hormone (PTH) in 101 patients operated on for solitary parathyroid adenoma (———) and in six patients with multiglandular disease (●) after excision of one enlarged parathyroid gland. The PTH levels were measured in 84 of the patients with adenoma and five patients with multiglandular disease at 5 min and in all 107 patients at 15 min. For the patients with solitary adenoma, values are mean(2s.d.); for patients with multiglandular disease individual values are indicated

Results

After operation all patients had normal or low calcium levels at a minimum follow-up of 1 year.

Of the 107 patients undergoing first-time exploration for pHPT, 101 had a solitary parathyroid adenoma and six patients had multiglandular disease. The median weight of the excised parathyroid adenoma in these patients was 0·75 (range 0·07–9·5) g. The mean(s.d.) decline in PTH level in the patients with primary exploration because of solitary adenoma was 63(17) per cent after 5 min and 83(10) per cent after 15 min (*Fig. 1*). With 95 per cent confidence the decrease in PTH level for patients with solitary parathyroid adenoma was at least 29 per cent from baseline value at 5 min and at least 63 per cent at 15 min. At 5 min, serum levels of intact PTH fell by more than 29 per cent in one patient with multiglandular disease. At 15 min, however, no patient with multiglandular disease had a decrease in PTH level of more than 60 per cent. At this point, the PTH level in three patients with solitary parathyroid adenoma decreased by 40, 54 and 55 per cent, and they were thus predicted not to have a solitary parathyroid adenoma. Their serum levels of calcium at the 1-year follow-up were 2·31, 2·23 and 2·21 mmol/l respectively. Using the authors' biochemical definition of a parathyroid adenoma, measurement of PTH at 5 min resulted in a sensitivity of 86 per cent, a specificity of 100 per cent and an overall accuracy of 86 per cent. At 15 min, the sensitivity was 97 per cent, the specificity 100 per cent and the overall accuracy 97 per cent.

There was no significant correlation between the preoperative serum level of total calcium and the decrease in

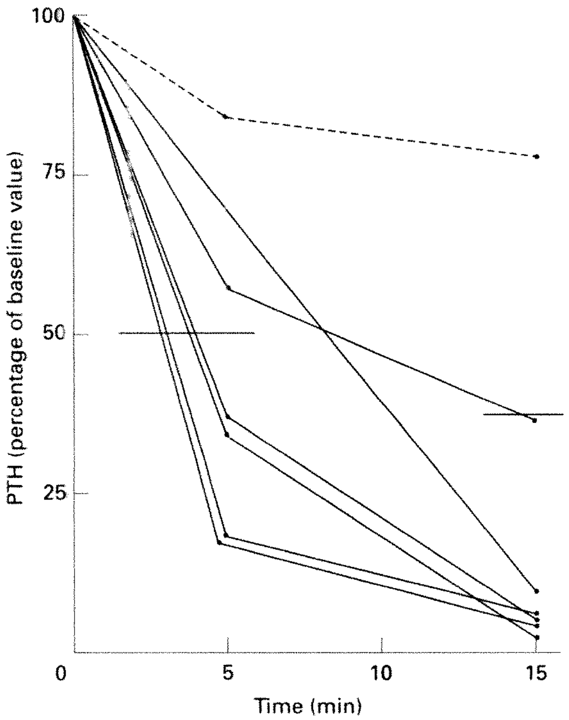

Fig. 2 Decline in intact parathyroid hormone (PTH) levels in seven patients with previous thyroid surgery at 5 and 15 min after excision of one enlarged parathyroid gland. Six patients had solitary parathyroid adenoma (———) and one patient had multiglandular disease (– – –). Bars denote the upper limit for a biochemical diagnosis of solitary parathyroid adenoma

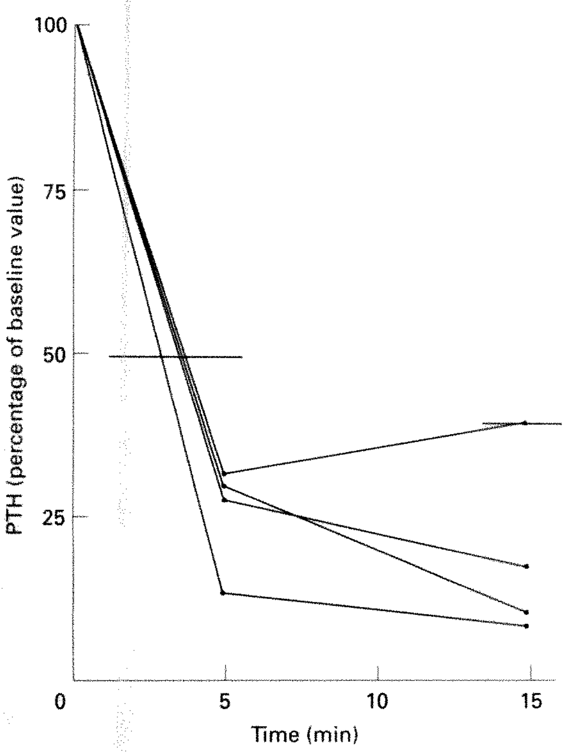

Fig. 3 Decline in intact parathyroid hormone (PTH) levels in four patients with persistent primary hyperparathyroidism with previous negative neck exploration at 5 and 15 min after excision of one enlarged parathyroid gland. Bars denote the upper limit for a biochemical diagnosis of solitary parathyroid adenoma

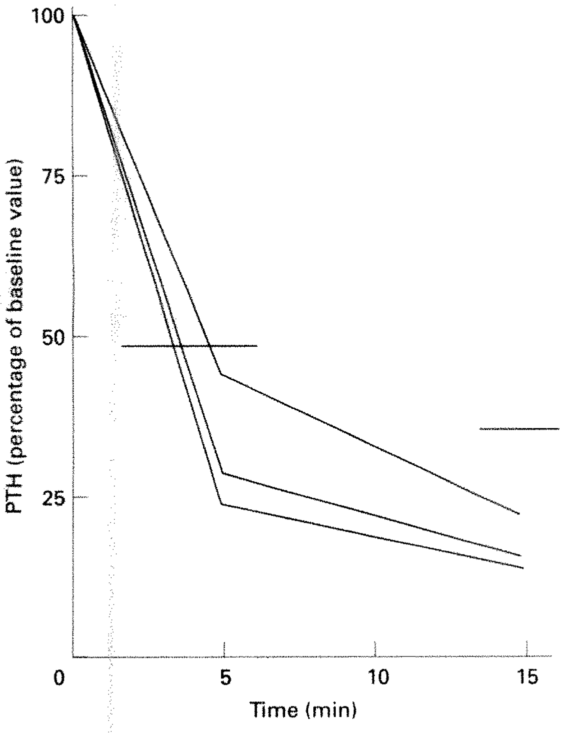

Fig. 4 Three patients with persistent or recurrent primary hyperparathyroidism with previous surgical excision of one enlarged parathyroid gland. The decrease in parathyroid hormone (PTH) levels is shown at 5 and 15 min after removal of a second enlarged gland during re-exploration. Bars denote the upper limit for a biochemical diagnosis of solitary parathyroid adenoma

intact PTH level at 5 min ($r = 0{\cdot}03$; $P = 0{\cdot}76$) and at 15 min ($r = 0{\cdot}03$; $P = 0{\cdot}74$). Eighteen (18 per cent) of the patients with solitary parathyroid adenoma had a serum level of calcium below 2·60 mmol/l (but in the high normal range) before operation. Their PTH level at 15 min after adenomectomy declined by 86(8) per cent.

There was also no correlation between preoperative serum level of intact PTH and the decrease in PTH at 5 min ($r = 0{\cdot}01$; $P = 0{\cdot}93$) and at 15 min ($r = 0{\cdot}05$; $P = 0{\cdot}68$).

In the seven patients with previous thyroid surgery, a solitary parathyroid adenoma was predicted by the decrease in PTH level in six and multiglandular disease in one patient (*Fig. 2*). After further exploration in this patient a second enlarged gland was found and removed. The decreased serum level of PTH at 5 and 15 min after removal of the second enlarged gland predicted that no hyperfunctioning tissue was left *in situ* at this point.

In the four patients who had previously undergone negative neck exploration, the decrease in PTH level after removal of the first enlarged parathyroid gland found predicted the excision of a solitary parathyroid adenoma (*Fig. 3*). In the three patients with previous excision of one enlarged parathyroid gland, removal of a second enlarged parathyroid gland during re-exploration resulted in a decrease in PTH level as for a solitary parathyroid adenoma and no further exploration was therefore performed (*Fig. 4*).

Discussion

The present investigation, based on 119 patients with pHPT, clearly shows that the intraoperative decline of intact PTH concentration is a highly sensitive and safe tool to differentiate between solitary parathyroid adenoma and multiglandular disease. The decrease in intact PTH level in patients with solitary parathyroid adenoma was, with 95 per cent confidence, at least 29 per cent from baseline value at 5 min and at least 63 per cent at 15 min.

At 5 min after gland removal the PTH level in one patient with multiglandular disease decreased by more than 29 per cent. The reason for this overlap is probably 'preanalytical'. For instance parathyroid gland manipulation, the time that it takes to draw the blood and inherent problems in determining the exact time zero could all contribute to a decreased accuracy of the test at this point. However, the biochemical definition of a solitary parathyroid adenoma (a decrease in PTH level of more than 50 per cent after 5 min and of more than 60 per cent after 15 min) provided a sensitivity of 86 per cent after 5 min and of 97 per cent after 15 min with a specificity of 100 per cent. With a decrease in PTH level of more than 50 per cent at 5 min after gland removal, the operation can therefore be terminated. In the remaining patients, the 15-min value must be awaited.

In the present investigation, no significant correlation was found between the decrease in PTH concentration and preoperative levels of serum calcium and intact PTH. In patients with solitary parathyroid adenoma and serum levels of calcium below 2·60 mmol/l (but in the high normal range) the PTH level decreased by 86(8) per cent at 15 min. The test can thus also be used reliably in patients with mild or intermittent hypercalcaemia.

The most important finding is the usefulness of the test in patients who have undergone previous neck surgery.

The intraoperative decrease in PTH level in all cases correctly predicted the return to normocalcaemia after operation.

The reliability of the test enables the surgeon to limit the surgical exploration and thereby reduce the risk of complications. In patients with persistent or recurrent pHPT and previous excision of an enlarged parathyroid gland, by definition having multiglandular disease, the decrease in PTH level after excision of a second enlarged parathyroid gland could show that no other hyperfunctioning tissue was left *in situ*.

For the rapid immunoradiometric PTH assay, the time for incubation is 20 min and the total turn-around time about 30 min. Good communication with the laboratory is therefore of utmost importance.

Recently, a immunochemiluminometric assay for rapid PTH measurement[15] has become commercially available. The incubation time for this assay is 7 min and the total turn-around time about 15 min. Since it does not suffer from the restrictions that accompany the use of radioisotopes, this assay could be used in the operating theatre.

In summary, intraoperative measurement of PTH during surgery for pHPT is a reliable method for differentiating between single and multiple gland disease as well as in patients with only mild or moderate aberrations in the serum calcium level. The on-line measurement is clearly clinically useful in patients with previous neck surgery. Its role in pHPT surgery at primary exploration, especially when performed according to the unilateral approach, needs to be evaluated in prospective randomized trials.

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Role of octreotide on release of intact 1–84 parathyroid hormone from human parathyroid cells

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Background Octreotide has been shown to lower urinary calcium in primary hyperparathyroidism although the mechanism remains unclear. This study examined the effect of octreotide on parathyroid hormone (PTH) secretion from human parathyroid cells in culture and as isolated cells. Additionally *in situ* hybridization was performed for somatostatin receptor messenger RNA (mRNA) and immunocytochemistry for somatostatin in eight parathyroid adenomas.

Methods Tissue from three hyperplastic glands and three adenomas was studied as dispersed cell suspensions. Incubation was in buffers containing high (2·0 mmol/l) and low (0·5 mmol/l) calcium concentrations, with or without octreotide 200 ng/ml. Cells were also seeded into tissue culture wells for 24 h to allow receptors to regenerate. Supernatant was removed at regular intervals and PTH levels were estimated using a two-site chemiluminescent assay.

Results Mean(s.e.m.) PTH secretion at 90 min in hyperplastic cells was 445(75) pmol/l in low calcium and 160(42) pmol/l in high calcium ($P < 0\cdot02$), and in adenoma cells was 170(21) pmol/l in low calcium and 137(27) pmol/l in high calcium ($P = 0\cdot37$). There was no significant difference in secretion of PTH from cells incubated with octreotide either in culture or as dispersed cells. *In situ* hybridization failed to demonstrate any mRNA for the somatostatin receptors and no somatostatin was detected in any cells with immunocytochemistry.

Conclusion Somatostatin has no direct action on PTH production and release from human parathyroid cells and is unlikely to be of any therapeutic value in the treatment of hyperparathyroidism.

Somatostatin is a tetradecapeptide that was first isolated from hypothalamic extracts during the search for growth hormone-releasing hormone and shown to be a potent inhibitor of growth hormone secretion from the anterior pituitary[1]. It is widely distributed, being found in the central nervous system and also peripheral tissues including stomach, intestine and pancreas[2]. Somatostatin was identified initially as a product of specific hypothalamic neurones, although subsequent studies demonstrated it to be the secretory product of the δ cells of the islets of Langerhans[3,4].

Somatostatin-14 is a member of a family of somatostatin-like peptides that also includes an amino terminally extended form, somatostatin-28[5]. The two principle bioactive forms of somatostatin, somatostatin-14 and somatostatin-28, are derived by tissue-specific proteolytic processing of prosomatostatin, a 92-amino-acid precursor, and are present in varying concentrations in different tissues[6].

As well as inhibiting the release of growth hormone, somatostatin has been shown to have a powerful inhibitory action on the release of a wide variety of regulatory peptides, leading to somatostatin being referred to as 'endocrine cyanide'[7–10]. Somatostatin has also been shown to significantly reduce splanchnic circulation through selective presplanchnic vasoconstriction[11,12].

Somatostatin-14 and somatostatin-28 exert their biological effects by binding to high-affinity receptors that appear in many cases to be coupled to guanosine 5′-triphosphate-binding proteins[13,14]. Pharmacological studies using the polymerase chain reaction indicate that there are at least five subtypes of receptor named SSTRI to SSTR5[15–19].

Soon after the discovery of somatostatin it became clear that the therapeutic value would be severely impaired by the short biological half-life of 2–3 min. Octreotide is a long-acting synthetic analogue of somatostatin, being 10 000 times more active in experimental conditions, and has been shown to be of value in treating acromegaly, pancreatic fistula, carcinoid tumours and haemorrhage from oesophageal varices[20–24].

As somatostatin exhibits inhibitory effects on a wide variety of secreted hormones, several workers have studied its effect on parathyroid hormone (PTH) release. In 1976, Deftos *et al.*[25] failed to demonstrate any effect of a somatostatin infusion on PTH release from six subjects with normal parathyroid function and one patient with a parathyroid adenoma. In contrast Hargis *et al.*[26] demonstrated suppression of PTH release in rats *in vivo* when somatostatin was infused, and also from bovine parathyroid and human adenomatous parathyroid cells cultured *in vitro* with somatostatin.

In patients with primary hyperparathyroidism (HPT) octreotide has shown no significant effect on serum calcium or PTH levels. Furthermore no evidence of octreotide binding to SSTR could be demonstrated in parathyroid tissue removed at operation from the same patients. One study, however, did demonstrate a decrease in urinary calcium levels and suggested that octreotide

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may have a place in the treatment of renal symptoms in these patients[27–29].

In light of the clinical data the current study posed three questions. (1) Does octreotide directly influence release of intact 1-84 PTH from human parathyroid cells? (2) Is the physiological ligand (somatostatin) demonstrable in parathyroid tissue? (3) Do parathyroid cells possess messenger RNA (mRNA) for somatostatin receptors? Three series of experiments were conducted. The release of intact 1-84 PTH from human parathyroid cells *in vitro* was studied, and immunocytochemistry for somatostatin and *in situ* hybridization for somatostatin receptor mRNA was performed in parathyroid tumours.

Materials and methods

Release of parathyroid hormone from human parathyroid cells

Fresh parathyroid tissue from three hyperplastic glands (removed because of secondary HPT in three different patients) and three adenomas was studied as dispersed cell suspensions.

The technique followed was originally described by Brown *et al.*[30]. Briefly, the tissue was digested with proteinase for 2 h resulting in a solution of isolated, viable parathyroid cells. The cells were resuspended in serum-free medium (DME/F12 with HEPES 15 mmol/l and L-glutamine without sodium bicarbonate; Sigma, Poole, UK) at a concentration of $2·5 \times 10^5$ per ml. The cells were then incubated in high (2·0 mmol/l) and low (0·5 mmol/l) calcium concentrations, with or without octreotide (Sandostatin; Sandoz, Basel, Switzerland) at a concentration of 200 ng/ml. Peak plasma concentration following a 50-µg subcutaneous injection is 2·25 ng/ml[31].

The theoretical possibility that the digestion processes might remove somatostatin receptors on the cell surface was controlled for by also seeding cells into tissue culture wells for 24 h to allow receptors to regenerate. Supernatant was removed at regular intervals and PTH levels were estimated using a two-site chemiluminescent assay for 1-84 intact PTH[32].

Immunocytochemistry for somatostatin in parathyroid adenomas

Wax-paraffin-embedded sections of eight parathyroid adenomas removed for primary HPT were studied. Sections of pancreas cut to display Islets of Langerhans were used as positive controls, the δ cells containing somatostatin. Serial sections from parathyroid adenoma to which primary antibody was not applied were also used to assess the degree of non-specific staining in tissue sections. A standard indirect immunocytochemistry technique was used. Washes were with phosphate-buffered saline (pH 7·2). Tissue sections were incubated with a primary mouse antisomatostatin monoclonal antibody (Sigma) for 16 h at room temperature. Following this, attached antibody was detected with an antimouse rabbit monoclonal antibody, conjugated to peroxidase (Sigma) and secondary antibody detected with the diaminobenzidine reaction. Nuclei were counterstained with haematoxylin before viewing the slides by light microscopy.

In situ *hybridization for somatostatin receptor messenger RNA in parathyroid tissue sections*

The eight adenoma samples in which immunocytochemistry for somatostatin had already been assessed were restudied. An antisense probe for detection of somatostatin receptor mRNA was selected from the complementary DNA coding sequence elucidated by Yamada *et al.*[18] and synthesized by B.B.L. (Abingdon, UK). The probe was designed to recognize the transmembrane-spanning region of the SSTRs, where the greatest homology has been found between the SSTR subtypes[33]. The 26-oligomer probe was labelled with digoxigenin according to the method of Farquharson *et al.*[34] resulting in a 5′-labelled probe: 5d′(GT CTT CAT CTT GGC ATA GCG CAG GAT)3′. Probe sequence specificity was checked through the EMBL (European Molecular Biology Laboratory) GenBank database.

Three control methods were employed. (1) Tissue known to be somatostatin receptor-positive was assessed for somatostatin receptor mRNA. The tissue was obtained from an adrenocorticotrophine hormone-producing tumour which had selectively localized with a radio-labelled octreotide scan. (2) A tissue section was included to which hybridization buffer containing no probe was applied. (3) For each tissue section examined, a second control slide of the same section was included to which an irrelevant probe was applied, antisense digoxigenin-labelled human papillomavirus 18 (HPV-18), an equimolar mixture of three 30-oligomer probes (BBL, Abingdon, UK).

Three serially sectioned slides were selected from each case and divided into two groups, test (one slide) and control (two slides). The *in situ* hybridization technique employed for mRNA staining was as described by Farquharson *et al.*[34]. Sections were incubated with hybridization buffer containing either the somatostatin receptor probe, HPV-18 probes or no probe at all. Some 20 µl of the buffer–probe mixture at a final concentration of 1·8 ng total oligonucleotide per µl was added per tissue section, which was then sealed under dimethydichlorosilane-coated cover slips. Slides were placed into a humid container for 16–18 h at 42°C. Following stringency washes, probes were detected using a conjugate mixture at room temperature for 1–2 h. Finally, the slides were washed and placed in an enzyme substrate solution in the dark for 13–15 h before the reaction was stopped by washing with distilled water several times. Slides were mounted in glycerol for viewing.

Results

Measurement of parathyroid hormone release from dispersed human parathyroid cells in culture

The results of PTH production are summarized in *Table 1* and displayed graphically in *Figs 1–3*. PTH production was significantly different at 90 min in hyperplastic cells cultured in high and low calcium concentrations ($P < 0·02$, *t* test). In adenoma cells no significant difference in PTH production was observed between different calcium concentrations ($P = 0·37$). There was no significant difference in production of PTH from either hyperplastic or adenomatous cells when incubated with octreotide either as dispersed cells or following culture.

Table 1 Parathyroid hormone secretion in tissue medium after incubation with or without octreotide

	PTH (pmol/l)	
	No octreotide	Octreotide (200 ng/ml)
Adenoma cells		
Low calcium (0·5 mmol/l)	170(21)	176(16)
High calcium (2·0 mmol/l)	137(27)	156(11)
Hyperplastic cells		
Low calcium (0·5 mmol/l)	445(75)	441(79)
High calcium (2·0 mmol/l)	160(42)	158(51)
Cultured adenoma cells		
Low calcium (0·5 mmol/l)	108(11)	103(9)
High calcium (2·0 mmol/l)	97(8)	94(10)

Values are mean(s.e.m.) concentration in tissue medium after 90 min (adenoma and hyperplastic cells) or 120 min (cultured cells) of incubation. PTH, parathyroid hormone

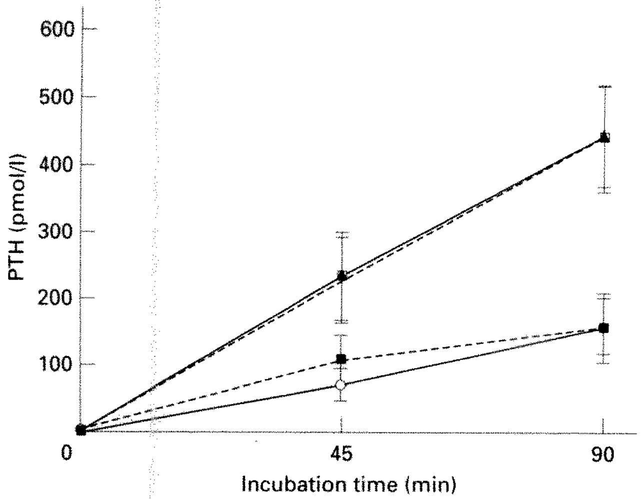

Fig. 1 Mean(s.e.m.) parathyroid hormone (PTH) production in isolated parathyroid cells from hyperplastic glands at varying concentrations of calcium ($n = 9$ per group). □, calcium 0·5 mmol/l; ○, calcium 2·0 mmol/l; ▲, calcium 0·5 mmol/l + octreotide 200 ng/ml; ■, calcium 2·0 mmol/l + octreotide 200 ng/ml

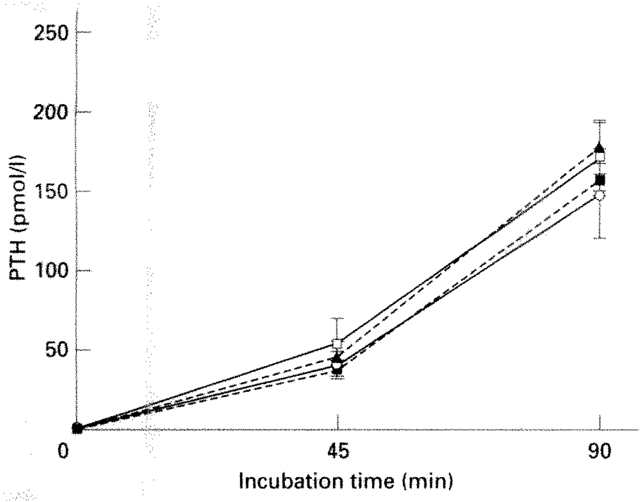

Fig. 2 Mean(s.e.m.) parathyroid hormone (PTH) in isolated parathyroid cells from adenomatous glands at various concentrations of calcium ($n = 9$ per group). □, Calcium 0·5 mmol/l; ○, calcium 2·0 mmol/l; ▲, calcium 0·5 mmol/l + octreotide 200 ng/ml; ■, calcium 2·0 mmol/l + octreotide 200 ng/ml

Immunocytochemistry for somatostatin in parathyroid adenomas

Positive immunocytochemical staining for somatostatin was clearly demonstrated in human Islets of Langerhans cells, the cytoplasm being characteristically stained brown, whilst nuclei were blue. Control sections remained clear with no evidence of any non-specific staining. None of the eight parathyroid adenomas reviewed showed evidence of either specific or non-specific immunocytochemical staining for somatostatin.

In situ *hybridization for somatostatin receptor messenger RNA in parathyroid tissue*

Positive staining of test slides compared with control slides was determined by several characteristic features: (1) granular texture of the cytoplasmic staining; (2) visible 'halo effect', i.e. no evidence of staining of the nucleus proper (nucleolar staining was ignored), with surrounding cytoplasmic staining; (3) staining confined to certain types of cell as opposed to all cell types; and (4) staining above that determined as background in control slides.

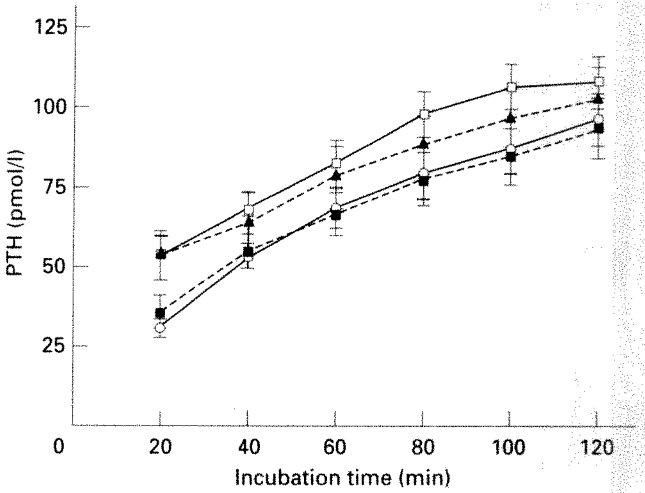

Fig. 3 Mean(s.e.m.) parathyroid hormone production in isolated parathyroid cells from adenomatous glands following culture for 24 h ($n = 9$ per group). □, Calcium 0·5 mmol/l; ○, calcium 2·0 mmol/l; ▲, calcium 0·5 mmol/l + octreotide 200 ng/ml; ■, calcium 2·0 mmol/l + octreotide 200 ng/ml

Positive staining for somatostatin receptor mRNA was clearly demonstrated in the tumour cells of the positive control specimen. There was no significant non-specific staining of mRNA by the irrelevant HPV-18 probe. Sections to which neither probe had been applied also showed no evidence of non-specific staining. None of the eight parathyroid adenomas examined showed any evidence of specific staining for somatostatin receptor mRNA or of non-specific probe binding.

Discussion

This study demonstrates that (1) octreotide has no influence on PTH secretion from either adenomatous or hyperplastic parathyroid cells maintained in culture for 24 h or as dispersed cells, (2) mRNA for somatostatin receptors is not detected in parathyroid cells and (3) immunocytochemistry for somatostatin is negative in parathyroid adenoma tissue sections.

Cells in this study obtained from parathyroid glands removed for secondary HPT maintained a degree of responsiveness to changes in external calcium concentration (*Fig. 1*). Cells obtained from adenomatous glands, however, appear to be autonomous in their function, showing no significant change in PTH release when subjected to alteration in calcium concentration of the medium (*Fig. 2*). This perhaps is to be expected when one considers the differing pathophysiology of the two conditions. Secondary HPT is a physiological response of the parathyroid glands to lowering of serum calcium from renal failure, whereas adenoma cells appear to have lost the ability to respond to changes in external calcium concentration and continue to produce PTH regardless, leading to primary HPT. It has been hypothesized that this may be due to a change in the set-point of the calcium-sensing receptor of the cell, leading to clonal proliferation and parathyroid adenoma formation in an effort to restore the calcium level to normal[35]. Neither group of cells, however, showed any change in PTH release when octreotide was added to the medium in supraphysiological doses.

By seeding cells into tissue culture wells and leaving them in complete tissue culture medium for 24 h, any somatostatin receptors stripped from the surface of the cell membrane during proteolytic digestion may, in theory, be allowed to regenerate. That adenomatous cells studied either as dispersed cells or following culture showed similar patterns of PTH secretion in high and low calcium concentrations suggests that the calcium-sensing receptor has not been stripped from the cell surface by enzymatic digestion. However, there was still no evidence of a change in PTH release when octreotide was added to the tissue medium (*Fig. 3*).

A potential flaw in this study may be that as octreotide binds only to receptor subtypes SSTR2 and SSTR5 no change in PTH secretion may be expected if parathyroid cells expressed any of the other receptor subtypes. However, all the cell culture experiments were repeated with somatostatin-14 which has a high affinity for all five SSTRs. The results are identical to those obtained with octreotide but for the sake of brevity and to avoid repetition the authors have omitted presenting the data in this paper.

Failure in this study to demonstrate the presence of somatostatin in any parathyroid tissue (none of eight tumours), suggests that the peptide is neither secreted nor absorbed by parathyroid cells. This is in contrast to other studies which have reported the presence of somatostatin-14 in 14 of 30 parathyroid adenomas and also the presence of a somatostatin-like immunoreactivity. The technique used, however, did not exclude the possibility that the somatostatin may not be localized in the parathyroid cells themselves but in the parathyroid nerves or blood vessels[36,37].

The area of greatest homology between the SSTRs is found in the transmembrane region, with greatest homology being noted between subtypes SSTR1 and SSTR4 on the one hand and subtypes SSTR2, 3 and 5 on the other. For this reason the *in situ* hybridization probe used in this study was designed to recognize a mRNA base sequence expressed in the transmembrane portion of SSTRs. No staining was demonstrated, however, for any SSTR mRNA in any of the eight adenomas studied. The lack of suitable surface receptors in parathyroid tissue strongly suggests that somatostatin plays no regulatory role in the secretion of PTH.

Administration of octreotide has been shown to have no effect on plasma levels of PTH *in vivo* either in healthy human volunteers or in those suffering from primary HPT[27–29,38]. Octreotide has, however, been shown to reduce urinary calcium in patients with primary HPT also with no observable effect on plasma PTH levels[27]. Similarly, reduced urinary calcium excretion and production of a positive calcium balance in patients with Duchenne muscular dystrophy has also been demonstrated. In these circumstances octreotide might act through somatostatin receptors known to be located in bone cells rather than by any direct action of somatostatin on the parathyroid glands[39].

In conclusion, the present study demonstrates that octreotide has no direct action on PTH release in patients with HPT and is therefore unlikely to offer any significant role in the treatment of this condition. Octreotide may have a possible role to play in the alleviation of some of the renal symptoms associated with HPT, although the effects appear to be of a secondary nature. Surgery will undoubtedly continue for the present to be the mainstay of treatment in HPT.

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Overexpression of p53 predicts shorter survival in diffuse type gastric cancer

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Background It has been suggested that p53 plays an important part in gastric carcinogenesis but the data remain inconclusive.

Methods Alteration of the tumour suppressor gene *p53* was prospectively investigated by immunohistochemistry in 168 primary gastric cancers.

Results Positive staining, indicative of gene mutations, was detected in 34 tumours (20·2 per cent). No correlation was observed between expression of p53 and various clinicopathological factors, including age, sex, tumour site, gross type, tumour size, depth of invasion, lymph node metastases, distant metastases, and tumour node metastasis stage. However, p53 overexpression was different between intestinal and diffuse type gastric cancer. Survival analysis revealed a significant survival disadvantage of p53 expression in diffuse type gastric cancer ($P = 0{\cdot}039$) but not in the intestinal type. Multivariate analysis of all 168 patients revealed that independent predictors of recurrent disease included age, invasion depth and nodal involvement but not p53 expression.

Conclusion The presence of p53 overexpression may identify a subset of more aggressive tumours with a poor prognosis in diffuse type gastric cancer.

It has been suggested that the most common genetic alternation in human cancers involves the loss of inhibitory function of the *p53* tumour suppressor gene product[1]. The *p53* gene mapped on chromosome 17p is an important negative regulator of normal cell growth and division. A common mechanism for this change appears to be the loss of one normal *p53* allele and point mutation of the remaining *p53* allele[2]. The resultant effect of these genetic alternations on intracellular p53 is a paradoxical increase in protein levels, since mutated p53 has a much longer half-life than normal p53. Accordingly, detectable levels of p53 protein product by immunohistochemistry suggest the existence of genetic alternations at this locus, since the very low steady-state levels of the normal protein (due to its rapid turnover) are usually invisible by this method[3]. Mutation of p53 and a raised protein level as determined by immunohistochemistry has been described in different types of human cancer[4–6].

Gastric cancer is a common disease worldwide and the third leading cause of cancer death in Taiwan[7]. Although aggressive surgical resection has improved the overall outcome of patients with this carcinoma, results of surgical resection for advanced cancer are still poor[8]. To search for predictors of disease survival and response to therapy is therefore mandatory. The molecular events leading to the development of gastric cancer are largely unknown, but there is now enough evidence to suggest that the functional inactivation of the *p53* gene through allelic loss and point mutation plays an important part[8–12]. Furthermore, several studies have shown recently that p53 mutations are likely to be associated with tumour metastases, stage and clinical outcome in breast cancer[13–16].

The aim of the present study was to determine whether p53 status in patients with gastric cancer patients who have undergone gastrectomy correlates with various clinicopathological characteristics and survival.

Paper accepted 6 November 1997

Patients and methods

Patients

Between July 1992 and December 1994, 168 patients who had undergone gastric resection for primary gastric adenocarcinoma were studied. No patient had undergone previous chemotherapy or radiotherapy and all patients were followed clinically for a median of 4 years. All the clinicopathological data were collected prospectively and registered in a database. The operation was performed according to the guidelines of the Japanese Research Society for Gastric Cancer[17]. Radical lymph node dissection ($R_{2/3}$) was performed routinely. A detailed histopathological examination was performed to determine the depth of invasion on the gastric wall and the extent of metastases within regional lymph nodes. The clinical stage was determined by the tumour node metastasis (TNM) system[18]. The histological diagnosis was made according to the classification of Laurén[19].

Immunohistological staining

Cancer and normal mucosa samples were taken immediately after surgical excision and snap frozen, then stored at − 70°C until use. For immunohistochemical demonstration of the p53 protein, sections of the freshly frozen tissues were cut at 6 µm and stained with specific monoclonal p53 antibody (Oncogene Science, New York, USA) by an avidin–biotin complex peroxidase complex method. Cryosat sections of 5–7 µm were cut and mounted on glass slides, then treated with 3 per cent hydrogen peroxide in methanol at room temperature for 30 min to block endogenous peroxidase. The tissue sections were then incubated for 20 min with normal non-immune goat serum from the same species as the secondary antibody. Excessive normal goat serum was blotted from the slides before incubation with the primary antibody. Sections were incubated with primary mouse monoclonal antibody against p53 gene product (Oncogene Science) at

1:50 dilution overnight in a moist chamber at 4°C. Sequentially, the sections were incubated with biotinylated goat antimouse antibody for 30 min at room temperature and peroxidase-conjugated streptavidin was applied for 10 min at room temperature. Tissue sections were then stained with 0·05 per cent 3′,3 diaminobenzidine tetrachloride freshly prepared in 0·05 mol/l Tris-hydrochloride (pH 7·6) containing 0·01 per cent hydrogen peroxide and checked by light microscopy to determine the colour of chromogen. Finally, sections were counterstained with Mayer's haematoxylin, or methyl green, and then mounted. The reaction was considered as positive when a strong colouration of the cell nucleus was evident. Negative control sections were processed immunohistochemically without the primary antibody and positive control sections were from a breast cancer known to express high levels of p53.

Statistical analysis

Data were analysed using the χ^2 test with Yates' correction and Student's t test to evaluate the statistical significance of the relationship between staging and other histopathological factors. Cumulative survival rates were calculated using the Kaplan–Meier method. Statistical differences between two survival curves were evaluated using the generalized Wilcoxon test and savage test. Multivariate analysis, Cox model of proportional hazards regression, was used to incorporate all of the explanatory variables with the greatest prognostic value[20]. $P < 0·05$ was considered to be statistically significant. The analysis was done using the Biomedical statistical package (BMDP Statistical Software, Los Angeles, California, USA).

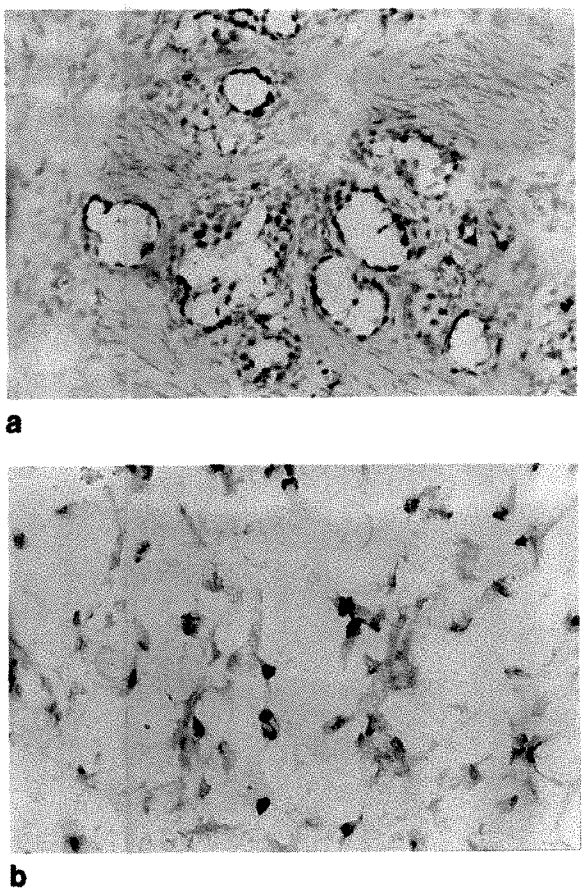

Fig. 1 Immunohistochemical staining of p53 protein in gastric cancer using monoclonal antibody. **a** Intestinal type cancer; p53 protein expression is seen primarily on cell nucleus (original magnification ×200). **b** Diffuse type cancer; cell nucleus staining is exhibited (original magnification ×400)

Results

Overexpression of p53

Nuclear staining of tumour cells was considered a positive p53 overexpression (*Fig. 1*). Nuclear positivity was not seen in any of the ten specimens of normal gastric mucosa used as controls or in the non-cancerous mucosa adjacent to the carcinoma.

An overall positive staining was seen in 34 (20·2 per cent) of 168 gastric cancers. The clinicopathological data relating to the resected tumours in both groups are summarized in *Table 1*. There was no significant correlation between p53 protein expression and any of the clinicopathological variables, including age, sex, tumour location, gross type, histological type, depth of invasion, lymph node metastases, distant metastases and TNM stage. Although p53 expression tended to be associated

Table 1 Association of p53 overexpression with clinicopathological findings in 168 patients with resectable gastric cancer

Variable	No. of patients	p53 negative	p53 positive
Total no.	168	134 (79·8)	34 (20·2)
Age (years)			
≤40	12	10 (83)	2 (17)
>40	156	124 (79·5)	32 (20·5)
Sex			
M	90	70 (78)	20 (22)
F	78	64 (82)	14 (18)
Location			
Upper	37	33 (89)	4 (11)
Middle	35	25 (71)	10 (29)
Lower	96	76 (79)	20 (21)
Macroscopic type			
Early cancer	23	20 (87)	3 (13)
Borrmann I	7	6 (86)	1 (14)
Borrmann II	22	17 (77)	5 (23)
Borrmann III	101	79 (78·2)	22 (21·8)
Borrmann IV	15	12 (80)	3 (20)
Size			
<4 cm	53	45 (85)	8 (15)
4–8 cm	89	70 (79·8)	19 (10·1)
>8 cm	26	19 (73)	7 (27)
Depth of invasion			
T_1	23	20 (87)	3 (13)
T_2	41	34 (83)	7 (17)
T_3	90	68 (76)	22 (24)
T_4	14	12 (86)	2 (14)
Lymph node metastases			
N_0	55	47 (85)	8 (15)
N_1	38	32 (84)	6 (16)
N_2	49	36 (73)	13 (27)
N_3	26	19 (73)	7 (27)
Distant metastases			
Negative	149	121 (81·2)	28 (18·8)
Positive	19	13 (68)	6 (32)
Histology			
Intestinal	72	54 (75)	18 (25)
Diffuse	83	69 (83)	14 (17)
Mixed	13	11 (85)	2 (15)
TNM stage			
I	39	31 (79)	8 (21)
II	26	23 (88)	3 (12)
III	65	52 (80)	13 (20)
IV	38	28 (74)	10 (26)

Values in parentheses are percentages. TNM, tumour node metastasis. No correlation was observed between p53 expression and any of these variables

Table 2 Comparison of p53 overexpression between intestinal and diffuse type gastric adenocarcinoma

Intestinal type + diffuse type ($n = 155$)	Intestinal type ($n = 72$)	Diffuse type ($n = 83$)
T_1 3 of 23	3 of 12	0 of 11
T_2 6 of 38	5 of 20	1 of 18
T_3 21 of 80	10 of 36	11 of 45
T_4 2 of 14	0 of 4	2 of 10

with advanced rather than early cancer (21·4 *versus* 13 per cent) and intestinal than diffuse cancer (25 *versus* 17 per cent), this had no statistical significance. A significant difference was found in the timing of p53 overexpression between the intestinal and diffuse type tumours; p53 expression was found in the early stage of intestinal type tumour but only in the late stage of diffuse type tumours (*Table 2*).

Prognostic relevance

Fig. 2a shows the survival curves of both groups after gastric resection. The survival rate of patients who had p53-positive tumours was lower than that of patients with p53-negative tumours but the difference was not statistically significant ($P = 0{\cdot}400$). The survival of 83 patients with diffuse type adenocarcinomas was analysed separately; a significant difference in survival was seen between patients with p53-positive and p53-negative tumours ($P < 0{\cdot}05$) (*Fig. 2b*). However, the presence of p53 was not a significant prognostic indicator in 72 patients with intestinal type cancer (*Fig. 2c*).

Multivariate analysis of all 168 patients revealed that age, invasion depth and nodal involvement but not p53 expression were independent prognostic variables. Multivariate analysis in 83 patients with diffuse type cancer revealed that only invasion depth was an independent and significant variable.

Discussion

Immunohistochemical techniques have revealed the presence of p53 protein in between 13·3 and 67 per cent of gastric carcinomas[21–32]. The rate of immunostaining for p53 in this study (20·2 per cent) was consistent with the rates of positivity mentioned above. The wide variation in the reported incidence of p53 immunostaining may be due to the various antibodies used in different reports and the difficulty of assessing specimens with low p53 expression. The incidence of p53 abnormalities appears to differ based on the histological type of cancer in previous studies. The present study also showed a higher percentage of p53 expression for intestinal type than diffuse type lesions, the difference was not significant. However, a significant difference in the timing of p53 overexpression between Laurén histological type was observed in this study as well as others[31,32]. This result implicates different carcinogenesis processes between these two types of gastric cancer.

In addition to epidemiological and pathological studies, recent reports have shown that intestinal type and diffuse type gastric cancer are two disease entities with different carcinogenic molecular events[33,34]. Intestinal type cancer, similar to colonic cancer, arises from the progression of

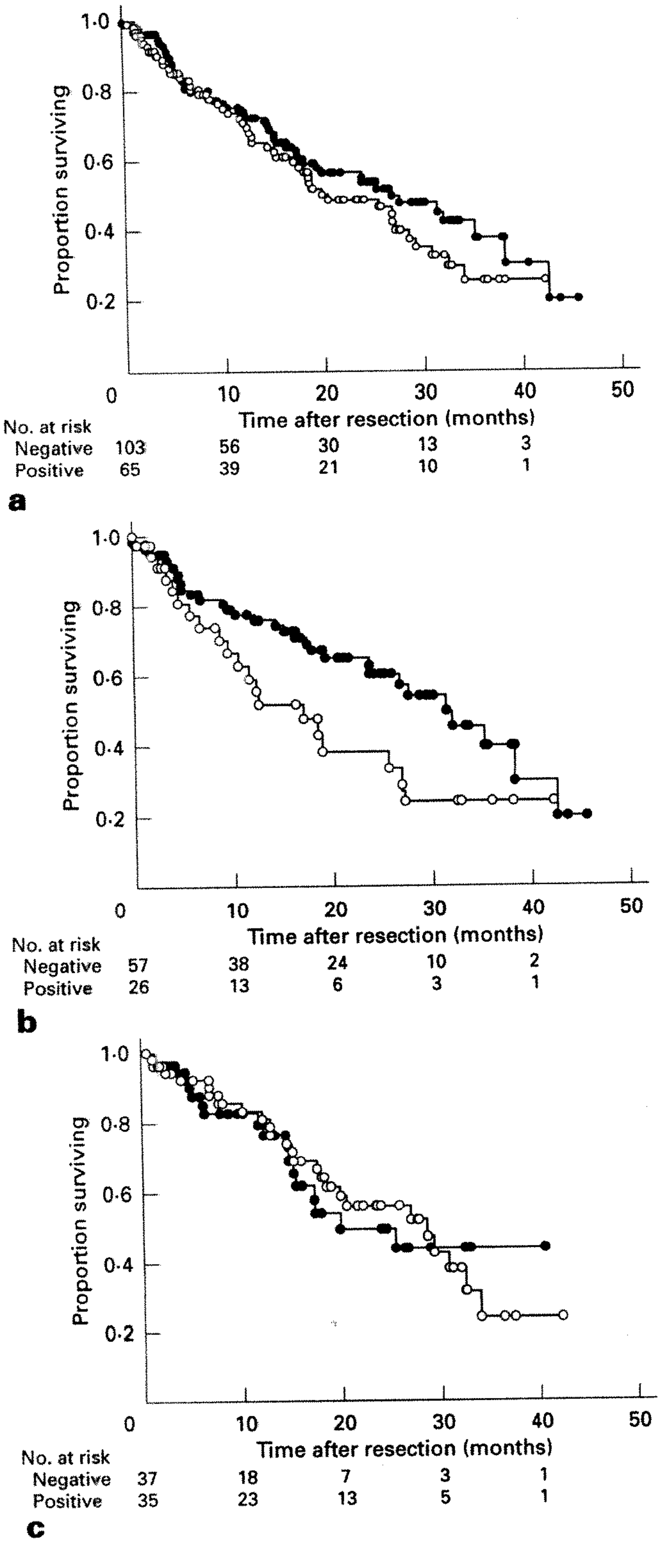

Fig. 2 Survival of patients after resection of gastric cancer. Cumulative survival curves were constructed for patients with p53-positive (○) or -negative (●) gastric carcinomas by the Kaplan–Meier method. **a** All 168 patients $P = 0{\cdot}400$ (generalized Wilcoxon test); $P = 0{\cdot}039$ (generalized savage test). **b** Eighty-three patients with diffuse type cancers. $P = 0{\cdot}045$ (generalized Wilcoxon test); $P = 0{\cdot}039$ (generalized savage test). **c** Seventy-two patients with intestinal type cancer. $P = 0{\cdot}66$ (generalized Wilcoxon test); $P = 0{\cdot}89$ (generalized savage test)

chronic atrophic gastritis, intestinal metaplasia and severe dysplasia. p53 mutations can be demonstrated in premalignant stages and early cancer of intestinal type cancer implying that alterations in p53 are not confined to the late stage for this subtype[25,30]. In diffuse type cancer, regarded as a kind of *de novo* cancer, p53 oncoprotein occurs in the late stage favouring cancer progression and metastases. Kakeji *et al.*[24] have reported that gastric cancer with p53 overexpression has a high potential for metastasizing to lymph nodes[24]. In the present study, there was no significant association between overexpression of p53 and lymph node metastases. However, that most metastatic lesions show positive p53 staining, even in patients with negative staining in primary tumours, corroborates with the finding of Kakaji *et al.*[24]. This could be explained by either a sampling error that might miss the mutation at the primary tumour site or by post-metastatic clinical divergence.

As for prognostic and p53 stainability, many reports have shown that p53 expression can serve as an independent prognostic indicator in the case of breast cancer[13–16]. Evidence for the prognostic relevance of p53 overexpression and gastric cancer is conflicting. Some authors have reported that their p53-positive cases behave more aggressively and have a worse prognosis[22,23,29], but conflicting data exist[26,27]. However, the prognostic relevance has not been compared between different histological types in previous reports and rarely by multivariate analysis. The present report shows that p53 overexpression is associated with significantly poorer survival in patients with diffuse type gastric cancer, suggesting that p53 expression identifies diffuse type carcinomas with a more malignant phenotype. Because multivariate analysis does not reveal p53 expression as an independent prognostic factor, the poorer prognosis for those with tumour expressing p53 may be attributed to a more advanced stage. In contrast, intestinal type gastric cancers are more frequently associated with p53 overexpression but without prognostic relevance. These carcinomas may use another mechanism for tumour progression, such as additional activated oncogenes or deletion of tumour suppressor genes. However, most of the patients present had advanced gastric cancer; p53 expression may still play a significant prognostic role in early gastric cancer when a large number of early cancers are analysed[35,36].

Identification of patients who have resectable high-risk disease is being increasingly taken into account by surgeons and oncologists. A large number of tumour biology-related factors have been investigated, but most have been evaluated retrospectively in paraffin-embedded material. It has been stressed that each factor that is supposed to have an impact on prognosis should be tested prospectively following curative resection in a multivariate analysis. This study evaluated the impact of a single biological factor on overall survival of gastric cancer. Further studies of other potential biological prognostic factors for gastric cancer following curative resection are indicated.

Because intestinal type and diffuse type gastric cancers may be regarded as two disease entities with different carcinogenic processes, it is possible that various biological indicators of tumour aggressiveness may play a different role in predicting the outcome of patients with these two types of gastric cancer[37,38]. It has been found that the ability of c-erbB-2 expression to predict survival is different between well differentiated and poorly differentiated gastric cancers[35]. The present study reveals that p53 expression is a prognostic indication of survival after complete resection of diffuse type gastric cancer but not in intestinal type cancer. In investigating the prognostic relevance of a new biological indicator it is mandatory to analyse these two types of gastric cancer separately.

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Active or passive chest drainage after oesophagectomy in 101 patients: a prospective randomized study

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Background This study evaluates the efficiency and safety of two methods of chest drainage after uncomplicated oesophagectomy.

Methods A prospective randomized study between active suction drainage and passive chest drainage was carried out in 101 patients who underwent gastric pull-up oesophagectomy.

Results No difference in the prevalence of pneumothorax during treatment was noted between the active (nine of 55) and the passive (four of 46) drainage groups ($P = 0{\cdot}20$). Nor was there any difference in the size ($P = 0{\cdot}46$) and duration ($P = 0{\cdot}53$) of the pneumothorax. There was no significant difference in right ($P = 0{\cdot}84$) and left ($P = 0{\cdot}61$) basal atelectases and the amounts of right ($P = 0{\cdot}10$) and left ($P = 0{\cdot}24$) pleural effusions. There were significantly more basal atelectases ($P < 0{\cdot}001$) and pleural effusions ($P < 0{\cdot}001$) in the non-operated left side compared with the operated right side. Postoperative hospital stay was the same in both groups (median 13 days; $P = 0{\cdot}86$). The hospital mortality rate was two of 101, and was not affected by the type of drainage.

Conclusion Passive drainage did not reduce hospital stay, but was as safe and effective as the active system in draining the pleural cavity after uncomplicated oesophagectomy.

Chest-tube drainage after transthoracic oesophagectomy is a necessary postoperative procedure to evacuate excessive amounts of fluid and air from the operated chest and to allow the lung to re-expand to provide adequate ventilation. Connection of the patient to a suction device in the wall reduces the patient's postoperative mobilization. In an attempt to provide postoperative mobilization, a passive pleural drainage system (Portex; Portex, Hythe, UK) was introduced, which eliminates the need to connect the patient to a wall suction device. The aim of the study was to evaluate the more easily handled passive underwater-seal drainage set by comparing it to a conventional active drainage system with respect to efficiency and security.

Patients and methods

From May 1990 to January 1996, 117 patients were admitted to the department of surgery for oesophagectomy. Before operation all patients were randomized to either an active suction drainage system ($n = 55$) or a passive drainage system (Portex; $n = 46$) for evacuation of the operated right chest. Thirteen patients were excluded because of irresectable tumours. Three patients who were randomized to the passive drainage system, but who later required active drainage because of postoperative complications, were excluded from the study. These three patients were excluded because the intention of the study was primarily to evaluate the different drainage methods in patients with an uncomplicated postoperative course. There were 72 men and 29 women operated on with an oesophagectomy and a gastric pull-up. Ninety patients were operated on because of malignant lesions and the rest for benign disorders. Malignant and benign disorders were equally distributed between the two groups ($P = 0{\cdot}17$, Fisher's exact test).

The abdomen was entered through an upper midline incision, and the stomach was isolated and transformed to a gastric tube with a linear stapling device, TLC 55 (Ethicon, Stockholm, Sweden) or GIA (Autosuture, Stockholm, Sweden). All operations were performed in a standardized way including fat and lymph node dissection in the upper abdomen and mediastinum. The thoracic oesophagus was explored through a right posterolateral thoracotomy, and the anastomoses were constructed in the apex of the right chest with a circular stapling device (Premium CEEA, cartridge size 25, 28 or 31 mm; Autosuture) or were manually sutured to the remaining oesophagus using polydioxanone (4/0 PDS II; Ethicon), through a separate cervical incision running parallel to the left sternocleidomastoid muscle. Two chest tubes (Argyle thoracic catheter, Charrière 28, Beiersdorf, Kungsbacka, Sweden) were inserted separately through the right inferolateral chest wall. One tube was placed anteriorly with the end close to the apex of the chest, and the second tube was placed in the posterior chest parallel to but 5 cm away from the oesophageal substitute, and fixed with a loop suture.

The active drainage set consisted of two connected reusable bottles which in turn were connected to a continuous suction device in the wall of the ward. The bottle connected next to the patient drained fluid. The pressure was regulated by the second bottle, which contained water and was connected to the suction device. The negative pressure was set to 15 cmH_2O, and was predetermined by adjusting the underwater level of the central metal rod through which the system communicated with the surrounding atmospheric pressure. The passive drainage bag system consisted of a smaller single-use 2000-ml lightweight plastic bottle, with an underwater seal for a one-way flow of the contents of the tubes.

Patients who were randomized to the passive drainage set were connected to this system on the first postoperative day as soon as they returned to the ward, where mobilization and physiotherapy was started. One specialized physiotherapist was responsible for the preoperative and postoperative pulmonary physiotherapy.

Postoperative bedside chest radiography was performed in the evening of the day of operation, on the third postoperative day, and as clinically necessary. When less than 200 ml of serous fluid was delivered through the drains in 24 h and there was no air leak the drains were clamped. Clamping usually began on the fifth postoperative day, after chest radiography in the erect position was done with lateral and anteroposterior projection to

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evaluate the degree of pneumothorax and the amounts of fluid. Another similar chest radiograph was obtained within the next 24 h to exclude pneumothorax before removing the chest tubes. Immediately before removal of the drains, but after the radiograph was taken, the clamps were removed and controlled active suction (15 cmH_2O) was connected to the chest drains during removal. This was done to equalize the intrapleural pressure in both groups, and to prevent pulmonary injury from excessive negative intrapleural pressure during drain extraction in the passive group. No complication was noted during the clamping procedure. A follow-up chest radiograph was taken the next day, as required, and always before the patient was sent home. At least five chest radiographs were obtained, normally on days 1, 3, 5, 6 and 7 after operation.

The radiographs were reviewed and evaluated by one radiologist (C.-G.L.) who was unaware of the method of drainage used. All but five radiographs were available at the time of evaluation. The degree (mm) and duration (days) of pneumothorax were determined by examining all the radiographs taken during the hospital stay. In the authors' previous experience 20 per cent of patients who underwent this procedure had a small pneumothorax in spite of well functioning drains, and the same proportion had pleural effusions. With the new disposable passive drainage system a reduction in the frequency of pneumothorax and pleural effusions to one tenth of the previous rate was anticipated. Power calculation showed that for an 80 per cent probability of detecting such a difference, 44 patients were needed in each group.

The size of pleural effusions was estimated on anteroposterior and lateral radiographic examinations performed in the upright position because the patients were not consistently examined in decubitus position. The degree of pleural effusion was graded from 0 to 3; grade 0, no effusion; grade 1, minimal effusion (1–2 cm), grade 2, 2–8 cm; and grade 3, more than 8 cm effusion. The rate of pleural effusions and atelectases were noted separately for each lung.

Nominal data were compared with Fisher's exact test. Data from the ordinal, interval and ratio scale were analysed using the non-parametric Mann–Whitney *U* test. $P < 0{\cdot}05$ was considered statistically significant.

Results

Median hospital stay was 13 (range 9–83) days in the active drainage group and 13 (range 8–41) days in the passive drainage group ($P = 0{\cdot}86$). The three patients in the passive drainage group who were excluded from the study had a hospital stay of 13–68 days. The chest drains were removed after a median of 7 (range 5–35) days in the active groups and 7 (range 4–33) days in the passive drainage group ($P = 0{\cdot}58$).

No difference in prevalence of pneumothorax during treatment was noted between the active (nine of 55) and passive (four of 46) drainage groups ($P = 0{\cdot}20$). After the removal of the chest drains seven patients in the active drainage group had a small remaining pneumothorax (5–25 mm) and one patient in the passive drainage group had a 10-mm pneumothorax ($P = 0{\cdot}07$, Fisher's exact test any pneumothorax or not). All resolved spontaneously. No difference was noted between the two drainage groups regarding the size ($P = 0{\cdot}46$) or the duration ($P = 0{\cdot}53$) of the pneumothorax. Forty-six (active drainage) and 42 (passive drainage) patients had no pneumothorax. Pneumothorax was median 10 (range 2–20) mm in the active group and 5 (range 2–10) mm in the passive drainage group. Pneumothorax persisted for 1 (range 1–4) days in the active group and 2·5 (range 1–5) days in the passive group. The distribution of right ($P = 0{\cdot}84$) and left ($P = 0{\cdot}61$) pulmonary atelectases and the amount of right ($P = 0{\cdot}10$) and left ($P = 0{\cdot}24$) pleural effusions was equal between the two drainage systems. Forty-seven of the patients had manually sutured cervical anastomoses while 54 patients had circular stapled anastomoses in the apex of the right chest. The type of anastomosis did not affect the distribution of pneumothorax, atelectases or pleural effusions ($0{\cdot}10 < P < 0{\cdot}84$). On the contrary, there were significantly more remaining basal atelectases ($P < 0{\cdot}001$) and pleural effusions ($P < 0{\cdot}001$) in the non-operated left chest compared with the right (*Table 1*).

Anastomotic leakage or gangrene or perforations of the oesophageal substitute, which could have affected the parameters studied, were noted in seven patients (*Table 2*). Because of these complications, three of the patients with passive drainages initially were converted to active suction drainage. These three patients were excluded from the study, but are reported in the table of complications (*Table 2*). The hospital mortality rate was two of 101; both patients who died were randomized to the active drainage group. One patient died during the operation from a cardiac arrest which was resistant to medical and mechanical treatment, and subsequently never had a chest

Table 1 Pulmonary atelectases and pleural effusions at the time of discharge in patients who underwent oesophagectomy

	Right side		Left side	
Grade	Active suction drainage ($n = 55$)	Passive suction drainage ($n = 46$)	Active suction drainage ($n = 55$)	Passive suction drainage ($n = 46$)
Atelectasis				
0	44	36	17	16
1	9	7	30	18
2	0	1	5	10
3	0	0	0	0
Missing	2	2	3	2
Pleural effusions				
0	40	39	15	18
1	13	5	29	21
2	0	0	8	4
3	0	0	0	1
Missing	2	2	3	2

Grading of atelectases: 0, no atelectases; 1, minimal atelectasis; 2, atelectasis covering approximately one or two segments; 3, atelectasis covering almost one lobe or more. Grading of pleural effusions: 0, no pleural effusion; 1, minimal pleural effusion (1–2 cm); 2, small pleural effusion (2–8 cm); 3, large pleural effusion (more than 8 cm)

Table 2 Postoperative deaths and complications after oesophagectomy in active or passive chest drainage groups

Hospital complications and death*	Active chest drainage ($n = 55$)	Passive chest drainage ($n = 46$)	Conversion to active from passive chest drainage ($n = 3$)
Anastomotic leakage			
No operation	0	1	0
Operation	0	1	0
Suspicion of leakage but negative chest exploration	1	0	0
Perforation in the transposed stomach			
No operation	0	1	1
Operation	1	0	1
Postoperative recurrent nerve palsy	1	0	1
Death from necrosis of the membranous part of the trachea	1	0	0
Cardiac arrest during the operation†	1	0	0

*Within 30 days. †This patient was randomized to the active drainage group but died before drainage was started

tube. The other patient died from a late necrosis of the membranous part of the trachea.

Discussion

Few publications have compared different drainage systems after chest surgery and to the authors' knowledge none after oesophagectomy and none in a highly standardized way. Alternative drainage systems such as the Heimlich valve[1] and other forms of drainage bags[2] have proved to be as good as the traditional glass bottle drainage system in chest surgery but the published series include different surgical procedures and unknown numbers and sizes of drains, making them hard to evaluate. Two drains of fixed diameter were used in the present study placed in a similar way after a standardized oesophagectomy.

The conventional active drainage system is safe but cumbersome to work with. The passive suction system is light, can easily be carried around by the patient and is easy for the staff to inspect and to handle. The passive drainage system is delivered sterilized and is a closed system which prevents migrating infections from the bottles, and has a scale for daily volume assessment. One disadvantage of the passive system is that the extent of negative intrapleural pressure varies with the amount of fluid in the chamber where the negative pressure is set. The manufacturer recommends a minimal and a maximal fluid content in this chamber, thereby assuring a proper pressure level. The fluid in the pressure-setting chamber empties automatically into a collecting chamber thereby regulating the pressure, so the maximum negative intrapleural pressure cannot reach extreme values. In the passive drainage system the actual negative intrathoracic pressure is unknown and beyond the control of the medical staff. According to the manufacturer, the negative intrapleural pressure in the passive drainage system at rest is between -2 and -5 cmH$_2$O, and during inspiration the negative intrapleural pressure decreases to about -35 cmH$_2$O[3]. If the negative pressure is reduced, for example after a coughing episode, a lower intrathoracic pressure may be set. This passive drainage method has not therefore been used routinely after anastomotic or substitute leakages. To prevent suction injuries, the posterior chest tube was anchored inside the right chest wall separately from the transposed stomach. No necrosis due to suction was noted in these patients. However, in one patient with a passive drainage set and in one in the active suction drainage group a chest tube was dislocated and the tip of the chest tube eroded the substitute with leakage as the result. Both leakages were treated successfully. It cannot be excluded that the negative pressure inside the drainage tube together with mechanical erosion from the tip of the drain resulted in the wounds described, but other factors such as defective vascular supply to the substitute may have contributed. It would be useful to be able to measure and correct improper pressure with the passive device.

The staying power of the passive drainage system seems to be as good as that of the active system because in both groups there were patients with pleural effusions of more than 200 ml per day for longer periods than a month, up to 33 days in the passive group and 35 days in the active drainage group. A clear advantage of the passive system is apparent in this respect: patients who are otherwise healthy but with a large amount of pleural drainage making removal of the drains impossible can after careful instruction leave the hospital.

The similar distribution of pneumothorax, frequency of pulmonary atelectases and pleural effusions, and median postoperative hospital stay between the groups indicated that passive drainage was as good as active drainage after oesophagectomy. Since the passive suction system did not immobilize the patient to the same extent, one might expect a shorter postoperative hospital stay in this group; however, this was not the case. To some extent this could be explained by the fact that the chest drains were removed after a median of 7 days in both groups. Thereafter the patients were immobilized for other reasons. The drainage tubes remained in place for about half of the postoperative hospital stay, and the period of recovery after removal of the tubes was unaffected by the method of drainage.

A clinically well known[4–6], and in this study well documented, difference was the dominance of basal atelectases and pleural effusions on the left side irrespective of the drainage system used. This was probably the result of the patient's position during the operation, with the left lung as the lowest point.

In conclusion, the light and convenient passive drainage bag system was as good and secure as the traditional active suction system for draining the right chest after uncomplicated oesophagectomy. There were no complications specifically attributed to the passive drainage system. Hospital stay was not affected by the type of drainage.

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Output of chyle as an indicator of treatment for chylothorax complicating oesophagectomy

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Background The management of chylothorax complicating oesophagectomy remains controversial. Even if medical management alone can be successful, some authors advocate early reoperation. The aim of this retrospective study was to identify the clinical variables associated with a high probability of full recovery with medical treatment.

Methods Among 850 Lewis procedures performed for oesophageal carcinoma, 23 patients (2·7 per cent) developed postoperative chylothorax despite systematic preventive ligation of the main thoracic duct. Patients who responded to conservative management were compared with those requiring reoperation for preoperative radiotherapy, unilateral *versus* bilateral pleural effusion, delay of occurrence of the chylothorax, and ratio of mean chylous output to body-weight 1 and 5 days after its onset.

Results Conservative management was successful in 14 patients with a mean(s.d.) delay of 12(5) (range 7–21) days and there were no hospital deaths. Reoperation was necessary in nine patients; there were two postoperative deaths and no recurrence of the chylothorax. The only significant difference between reoperated and medically treated patients was the mean(s.d.) chylous output at day 5: 23·5(16·6) *versus* 6·7(5·5) ml per kg body-weight ($P < 0·001$). At this time, the output was less than 10 ml/kg in 12 of 14 patients in whom medical treatment was successful (sensitivity 86 per cent), and equal to or greater than this cut-off value in all the patients who underwent reoperation (specificity 100 per cent).

Conclusion The ratio of chylous output to body-weight on the fifth day after the onset of a chylothorax complicating oesophagectomy seems to reliably predict the success of continuing medical treatment.

The close anatomical relationship between the oesophagus and the main thoracic duct explains the risk of chylothorax after oesophageal resection. Despite improvement in postoperative nutritional support, chylothorax complicating oesophagectomy remains a serious condition which may jeopardize immunological and nutritional status which is often already severely impaired in patients with cancer[1]. Primary management of chylothorax usually requires chest drainage and total parenteral nutrition[2–6]. However, the morbidity and variable efficacy of medical treatment have caused some authors to suggest early reoperation in the first week following the onset of chylothorax[7–9]. The drawback of this aggressive approach is that thoracotomy is performed a few days after the initial operation in a patient who might have recovered with conservative management. Therefore, the optimal management of postoperative chylothorax is still not clearly defined. The aim of this study was to identify early clinical variables allowing accurate indications for medical treatment or reoperation in patients with chylothorax complicating oesophagectomy.

Patients and methods

Between 1980 and 1996, 850 patients underwent a Lewis procedure for oesophageal carcinoma at this institution. During the thoracic phase, oesophageal resection included extensive lymphatic clearance with complete posterior mediastinectomy from the diaphragm to the aortic arch. The extent of supra-aortic lymph node dissection was based on the level of the tumour and the surgeon's preference. All patients underwent supradiaphragmatic ligation of the main thoracic duct posterior to the aorta along the front of the spine with a non-absorbable suture. Patients who underwent oesophagectomy without thoracotomy or cervical oesophagogastric anastomosis with cervical lymph node dissection were excluded because the extent of lymph node clearance was more variable.

Postoperative chylothorax developed in 23 patients (2·7 per cent) who were the basis of the study. There were 19 men and four women with a mean(s.d.) age of 54(11) (range 34–73) years. The diagnosis of chylothorax was suspected as early as the third postoperative day when the chest drainage output was greater than 500 ml per 24 h with a lymphocyte count of more than 50 per cent[9]. The diagnosis was confirmed by injection of a cream-rich diet through the nasogastric tube which resulted in a milky appearance of the pleural fluid. Initial management always included unilateral or bilateral chest drainage and total parenteral nutrition which was begun as soon as the diagnosis of chylothorax was established. Throughout the period of this study, the policy was to continue medical treatment for at least 12 days after which reoperation through the previous right thoracotomy was attempted if daily chylous output was greater than 500 ml or the lung was not re-expanded. Lymphography was not performed before reoperation. A cream-rich diet was given before operation to facilitate localization of the chylous leak.

The influence of five variables on the outcome of postoperative chylothorax was analysed including: preoperative radiotherapy, bilateral pleural effusion, delay of onset of chylothorax after oesophagectomy, and ratio of chylous flow to body-weight on day 1 and day 5 following the onset of chylothorax[1,10].

Data are expressed as mean(s.d.). The Mann–Whitney *U* test was used to compare non-parametric data. Other data were compared by the χ^2 test. $P < 0·05$ was considered to be statistically significant.

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Results

Conservative treatment resulted in recovery in 14 patients. In these patients, chest drainage was stopped after 9(5) (range 3–17) days and food intake was begun within 12(5) (range 7–21) days without recurrence of the chylous effusion. Conservative treatment was complicated in one patient who developed sepsis from the central venous access.

In nine patients, conservative treatment did not successfully stop the chylous leak. These patients were reoperated after 18(6) (range 12–27) days. In eight patients, the leak was located on the right side of the descending aorta or at the aortic arch. These patients underwent a more caudal repeat ligation of the thoracic duct. Ligation included all surrounding tissue, and was associated with direct suture of a visible leak in five patients. In another patient, the chylous leak originated on the left side of the descending aorta from lymphatic ducts which were ligated. Pleural decortication was performed in five reoperated patients. Seven patients had an uneventful postoperative course. Two reoperated patients died from sepsis related to an anastomotic leak, without recurrence of the chylothorax. One of these leaks was discovered at the time of repeat thoracotomy while the other developed after reoperation.

Table 1 Characteristics of patients with postoperative chylothorax who underwent medical or surgical treatment

	Not reoperated (*n* = 14)	Reoperated (*n* = 9)	*P*
Preoperative radiotherapy	4	3	0·58*
Bilateral effusion	3	1	0·48*
Delay of onset of chylothorax (days)*	4·9(3·9)	5·7(2·9)	0·29†
Chylous output to body-weight ratio (ml/kg)*			
Day 1	21·4(15·8)	27·6(15·1)	0·36†
Day 5	6·7(5·5)	23·5(16·6)	0·0004†

*Values are mean(s.d.). *χ^2 test; †Mann–Whitney *U* test

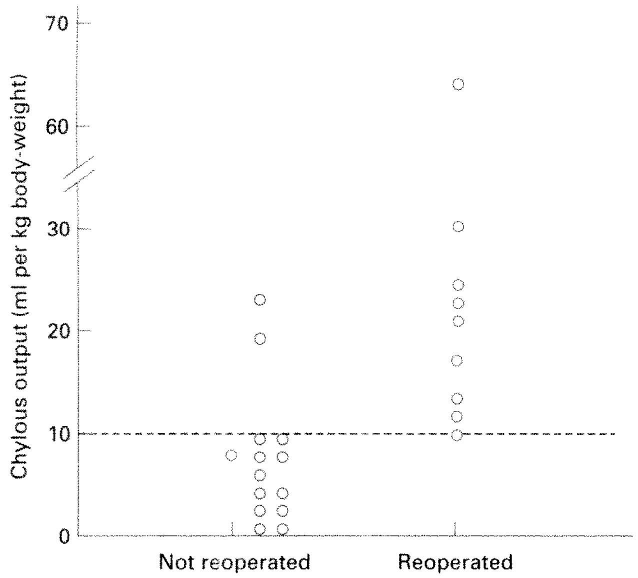

Fig. 1 Distribution of the daily chylous output to body-weight ratio on day 5 after the onset of chylothorax in non-reoperated and reoperated patients

Characteristics of patients in whom conservative treatment was successful and of those who required reoperation are summarized in *Table 1*. On the fifth day following the onset of chylothorax, the mean chylous output to body-weight ratio was significantly lower in patients who were treated conservatively than in those in whom a subsequent reoperation was performed. Chylous outflow on the fifth day of medical treatment was below 10 ml/kg in 12 of the 14 patients who did not require reoperation (sensitivity 86 per cent) and equal to or greater than this cut-off value in all the patients who did undergo reoperation (specificity 100 per cent) (*Fig. 1*).

Discussion

In the present study, a daily chylous loss of 10 ml/kg at day 5 after the onset of the chylothorax was reliable for differentiating patients in whom medical treatment succeeded from those who had a reoperation. Reoperation was avoided in all patients with a chylous output less than this cut-off value. In contrast, in patients with a chylous output exceeding this cut-off value, indication for reoperation should be balanced by the mortality rate observed in the present series (two of nine patients). Patients were selected for reoperation on the volume of output, and it is possible that some chylous leaks may have closed spontaneously in this group.

For most authors, management of chylothorax requires chest drainage and total parenteral nutrition[2–6]. Conservative management alone allows closure of the fistula in up to 80 per cent of patients within 2–5 weeks but can lead to some metabolic and septic complications when sustained[4,5]. In the series of Marts *et al.*[5], the mean duration of medical treatment alone was 13 days and the mortality rate was 8 per cent. In contrast, Bolger *et al.*[4] reported a 50 per cent mortality rate when the treatment lasted for a mean of 35 days. In the present series, no patient died with conservative treatment; this result probably reflects the short duration of the treatment, which lasted a mean of 12 days in patients who were treated conservatively and 18 days in reoperated patients.

To minimize the adverse effects of chylothorax, some authors have suggested rapid reoperation to close the chylous leak no later than 1 week after its occurrence[7,8,11]. Early reoperation allows easy localization of the leak before postoperative adhesions have developed. The success rate of reoperation was as high as 90 per cent with no hospital deaths in a series of 11 cases of chylothorax complicating 320 transhiatal oesophagectomies[7]. This result does not seem to be directly applicable to the present patients. In Orringer's series[7], the lack of previous thoracotomy probably facilitated access to the mediastinum and allowed ligation of the duct without exposing the cervical anastomosis. In patients with a thoracic anastomosis, reoperation can be harmful as suggested in one patient in the present study who developed fatal anastomotic leakage 2 days after reoperation.

Some groups have defined criteria for reoperation after failure of medical treatment. Preoperative radiotherapy, which has been suggested to increase the prevalence of postoperative chylothorax[12], did not influence the need for reoperation in the authors' experience. A bilateral pleural effusion[6] was not more frequent in reoperated patients of the present series than in those who did not undergo reoperation. For Patterson *et al.*[13], operation is indicated if a daily chylous loss of 1 litre or more persists for more than 1 week. Teba *et al.*[3] recommend reoperation for a chylous loss exceeding 1·5 litres per day for 5 days or persisting for more than 2 weeks. The onset of nutritional complications is also an indication for surgery[2]. The authors' policy was to continue medical treatment for a minimum of 12 days before undertaking a repeat thoracotomy, since this delay was considered to be optimal for anastomotic healing, the onset of adhesions and an effective duration for medical treatment. The results of the present study suggest that reoperation may be decided after the fifth day of medical treatment. However, the optimum delay before performing reoperation with a low rate of complications cannot be determined from this study.

In the present series of 850 patients from a single centre there was a 2·7 per cent rate of chylothorax complicating a Lewis procedure despite systematic preventive ligation of the main thoracic duct. This result is comparable to that of Dougenis *et al.*[8] who reported a 2·1 per cent rate of chylothorax after oesophagectomy including preventive ligation of the main thoracic duct. Anatomical variations encountered in up to 40 per cent of patients[14,15] probably explain the chylous leak located on the left side of the descending aorta which was observed in one reoperated patient. In the eight other reoperated patients, the cause of the chylous leak was a technical failure. In these cases, the ligation was either too cranial in the mediastinum or too restricted and did not include all the collaterals of the main thoracic duct. In these eight patients, a repeat ligation which included all tissues located between the right side of the aorta, the spine and the mediastinal pleura was performed successfully[16].

In conclusion, medical management was successful in 14 of 23 patients who developed chylothorax after a Lewis procedure including preventive ligation of the main thoracic duct. A daily chylous output of less than 10 ml/kg after 5 days of medical treatment is reliable for predicting successful medical treatment which in this study occurred within a mean of 12 days. Otherwise, reoperation by repeat thoracotomy should be planned taking into account its associated mortality rate.

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Clinical features and investigations in patients with columnar-lined oesophagus

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Background It is unclear why some patients with a columnar-lined oesophagus present with intestinal metaplasia and others do not. The physiopathological and clinical implications of the length of the metaplastic segment are also controversial. The aim of the study was to determine whether the length of the metaplasia and the presence of intestinal epithelium are related to the clinical, manometric and pHmetric data in patients with columnar-lined oesophagus.

Methods A comparison of clinical, endoscopic, pathological, manometric and pHmetric data was made between patients with columnar-lined oesophagus of 3–5 cm ($n = 31$) and those with a metaplastic segment of 5 cm or more ($n = 28$); the same comparison was made between patients who had specialized intestinal metaplasia ($n = 37$) and those who did not ($n = 22$).

Results No significant difference was found in any of the variables studied except for associated inflammatory lesions above the columnar epithelium which were more frequent in patients with a shorter metaplastic segment ($P < 0{\cdot}05$).

Conclusion Neither the length of the metaplastic segment nor the presence of intestinal metaplasia was related to a more evolved gastro-oesophageal reflux disease, a poorer oesophageal clearing function or higher acid reflux rates.

It is unknown why some patients with a columnar-lined oesophagus develop intestinal metaplasia and others do not. It is also unclear why the length of the metaplastic segment varies greatly between patients, there being little information in the literature on the determining factors. The duration of symptoms, presence of bile and pancreatic juice in the refluxed material, toxic habits (smoking, alcohol etc.) and individual factors (age, sex, heredity) may be involved.

The aim of this study was to investigate in a group of 59 patients with circumferential columnar-lined oesophagus whether the length of the metaplastic segment and the presence of specialized epithelium are related to the patients' epidemiological, clinical, endoscopic, histological, manometric and pHmetric data.

Patients and methods

The current concept of Barrett's oesophagus includes not only cases of circumferential metaplasia, over 3 cm in length and continuing into the cardia[1], but also those which, arranged in tongues or islets or measuring less than 3 cm in length, present with intestinal or specialized metaplasia[2]. This redefinition underlines the importance of intestinal metaplasia as a premalignant lesion. However, as this study was carried out in 59 patients diagnosed with columnar-lined oesophagus between January 1982 and January 1993 in this department, it does not include those patients currently defined as having 'short Barrett's'[3]. In all the patients endoscopy showed a circumferential metaplasia of over 3 cm in length in the distal oesophagus and continuous with the cardia, which was confirmed histologically.

To assess the importance of the length of the metaplastic segment the patients were divided arbitrarily into two groups: group 1 ($n = 31$) when the length of the metaplasia was between 3 and 5 cm, and group 2 ($n = 28$), when it was 5 cm or more. In the same way, to assess the importance of the intestinal metaplasia, the patients were divided into another two groups according to whether they presented with intestinal columnar-lined oesophagus (ICLO) ($n = 37$) or gastric columnar-lined oesophagus (GCLO) ($n = 22$) epithelium in the biopsies of the metaplastic segment. All patients underwent clinical, endoscopic, histological, manometric and pHmetric assessment.

Clinical assessment was done by personal interview using a questionnaire. Smokers or ex-smokers of more than five cigarettes per day fell into the 'smoking' group. Alcohol intake exceeding 280 g per week or 40 g per day in men, and 168 g per week or 24 g per day in women was considered as 'alcohol abuse'.

Endoscopy was performed in all patients by the same endoscopist using a flexible fibre endoscope (Olympus q-10, Tokyo, Japan). The following reference points were taken: incisors, squamocolumnar junction (Z line) and cardia. The cardia was identified by the highest gastric fold and by the interruption of deglutition waves. The hiatus was also identified in all cases, a hiatus hernia being present in all but one patient. The length of the metaplastic segment was calculated by subtracting the distance from the incisors to the proximal edge of the metaplastic segment and that of the cardia. Biopsies were taken systematically as follows: the first four samples (one in each quadrant) immediately proximal to the squamocolumnar junction, the next four immediately distal to the same, and the rest at 2-cm intervals in a caudal direction in each quadrant. Also considered for the study were endoscopic data on the presence of Barrett's ulcers, stenosis and oesophagitis. The median number of biopsies was 12 (range 12–20) in group 1 and 16 (range 16–24) in group 2. All biopsies were studied by the same two expert pathologists with an interest in Barrett's oesophagus.

The biopsies were analysed histologically by haematoxylin–eosin staining. The metaplasia was classified into four variants[4]: fundic, junctional, intestinal and mixed (when there was a combination of the others).

Twenty-four-hour pH monitoring and oesophageal manometry were performed in all patients. The characteristics of the equip-

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ment and method used in both tests have been described previously[5].

Data are presented as mean(s.d.). Comparisons of means were made by the Wilcoxon non-parametric test. Comparison of the frequencies of qualitative variables in independent samples was made by χ^2 test with Fisher's exact test where necessary. Differences were considered statistically significant when $P<0·05$.

Results

As far as the length of the columnar-lined oesophagus is concerned, no differences were found in the ratio of sexes, age, percentage of smoking or alcohol abuse, initial symptoms or duration of symptoms (*Table 1*). Patients with a shorter columnar-lined oesophagus had a greater percentage of associated inflammatory lesions above the metaplastic segment ($P<0·05$). No other significant differences were found regarding other peptic complications associated with the columnar-lined oesophagus, such as ulcers and/or stenosis (*Table 2*). Patients with a longer metaplastic segment did not show a greater prevalence of intestinal metaplasia.

The manometric study revealed a defective lower oesophageal sphincter (LOS) in both groups, but with no significant differences. There was no difference in the motor function of the distal oesophagus. Twenty-four-hour pH monitoring showed pathological rates of acid gastro-oesophageal reflux in both patient groups, with no statistically significant differences between them (*Table 3*).

Discussion

Although it is generally accepted that columnar-lined oesophagus is a condition acquired as a result of severe prolonged gastro-oesophageal reflux, Little[6] has suggested that the origin of the metaplasia could depend on its length. According to this author, metaplastic segments of less than 5 cm in length would probably be related to pathological gastro-oesophageal reflux, whereas longer metaplastic segments would represent congenital or developmental alterations. The present data suggest that the length of the metaplasia is not related to symptoms or their duration, which is in agreement with Cameron *et al.*[7–9], who claim that the columnar-lined oesophagus quickly attains a certain length and then becomes stable.

From a functional point of view, Mason and Bremner[10] relate the spread of metaplasia to impaired motor function of the oesophageal body (smaller amplitude and

Table 1 Epidemiological and clinical data

	Metaplastic segment (cm)			
	3–5 ($n=31$)	≥5 ($n=28$)	ICLO ($n=37$)	GCLO ($n=22$)
Sex (M:F)	20:11	20:8	28:9	12:10
Mean(s.d.) age (years)*	36·2(18·4)	39·3(18·6)	37·6(16·2)	37·8(20·1)
Smoking	11	10	15	6
Alcohol abuse	8	7	11	4
Heartburn	28	25	34	19
Dysphagia	17	13	19	11
Pain	11	7	10	8
Dyspepsia	8	4	9	3
Mean(s.d.) duration of symptoms (years)*	18·1(13·5)	16·7(14)	17·8(12)	17·6(13·9)

ICLO, intestinal columnar-lined oesophagus; GCLO, gastric columnar-lined oesophagus. None of these observed differences was statistically significant. *Wilcoxon non-parametric test (χ^2 test for comparison of frequency of qualitative variables in dependent samples)

Table 3 Manometric and pHmetric data

	Metaplastic segment (cm)			
	3–5 ($n=31$)	≥5 ($n=28$)	ICLO ($n=37$)	GCLO ($n=22$)
TLLOS (cm)	2·3(0·9)	2·4(0·8)	2·5(0·9)	2·2(0·8)
ALLOS (cm)	0·4(0·5)	0·5(0·6)	0·5(0·6)	0·4(0·5)
LOSBP (mmHg)	6·8(4·5)	7·5(5·5)	8·3(5·1)	6·0(4·4)
APW (mmHg)	40·4(24·3)	37·0(40·3)	34·5(31·2)	43·0(31·3)
%TW	24·9(36·9)	35·9(40)	24·2(33·7)	33·7(41·8)
%DWR	22·5(26·8)	26·0(35·9)	27·4(33·4)	20·9(27·9)
%TT pH < 4	19·6(14·6)	25·3(18·1)	22·4(11·5)	22·2(19·1)

Values are mean(s.d.). ICLO, intestinal columnar-lined oesophagus; GCLO, gastric columnar-lined oesophagus; TLLOS, total length of the lower oesophageal sphincter (LOS); ALLOS, abdominal length of the LOS; LOSBP, basal pressure of the LOS; APW, amplitude of peristaltic waves; %TW, percentage of tertiary waves; %DWR, percentage of deglutitions without response; %TT pH < 4, percentage of total time with pH less than 4. There was no statistically significant difference (Wilcoxon non-parametric test)

Table 2 Endoscopic findings (peptic complications) associated with metaplasia

	Metaplastic segment (cm)							
	3–5 ($n=31$)	≥5 ($n=28$)	χ^{2*}	P	ICLO ($n=37$)	GCLO ($n=22$)	χ^2	P
Oesophagitis	24	11	7·36	0·007	22	13	0·06	0·806
Stenosis	16	14	0·02	0·891	16	14	1·55	0·213
Ulcer	2	6	1·68	0·195	7	1	1·36	0·244
Specialized metaplasia	19	18	0·001	0·975	—	—	—	—

ICLO, intestinal columnar-lined oesophagus; GCLO, gastric columnar-lined oesophagus. *Values for χ^2 with 1 d.f.

longer duration of peristaltic waves), suggesting 'a progressive deterioration of oesophageal motility with advanced disease'. These authors thus establish a parallel between the length of the metaplasia, stage of the disease and degree of deterioration of motor function. The present results, however, do not support this statement since the group of patients with a longer metaplastic segment did not have a more defective LOS, a poorer clearing function of the oesophageal body or higher rates of gastro-oesophageal reflux. The discrepancy with Mason and Bremner's data may be related to the fact that they did not study LOS pressure or quantify gastro-oesophageal reflux, and could have been comparing two groups of patients with different reflux rates.

Special consideration should be given to patients currently regarded as having 'short Barrett's'[3], i.e. lesion less than 3 cm in length but with histological evidence of intestinal metaplasia, in many cases without endoscopic signs or symptoms of reflux disease. Little is known about the relation of short Barrett's to gastro-oesophageal reflux and its possible neoplastic degeneration. This study does not include such patients, since the classical definition of 'Barrett's oesophagus' was used. However, for Spechler and Goyal[3], the presence of specialized-type epithelium, the neoplastic potential of which is widely documented, is a condition that is not only sufficient, independent of its length, but necessary for diagnosing Barrett's oesophagus. Therefore, their concept of 'Barrett's oesophagus' would exclude patients with long segments of columnar-lined oesophagus in which only the presence of gastric-type epithelium is detected. In the present study, the patients with specialized-type epithelium did not have longer-lasting symptoms or greater deterioration of oesophageal function. Moreover, the rate of acid gastro-oesophageal reflux was similar in patients with gastric-type and intestinal-type epithelium. Thus it is unclear why some patients develop a columnar-lined oesophagus with intestinal-type metaplasia and others with the same physiopathological condition (advanced gastro-oesophageal reflux disease), develop the gastric type. Other factors may be involved such as biliopancreatic reflux to the oesophagus[11,12], the severity of the initial lesion in the epithelium or the intimate differentiation mechanisms of the pluripotential cells that cause the metaplasia[13–15]. It has been suggested that the longer the metaplastic segment the more frequent the presence of intestinal metaplasia[3], although in this study no significant relation was found between these two variables, and the possibility of there being areas of intestinal metaplasia within the segment of columnar metaplasia that have gone unnoticed seems remote, considering the number of biopsies performed. Furthermore, a number of reports[16,17] describe patients with columnar-lined oesophagus extending well up the oesophagus in whom biopsy specimens showed only junctional or gastric fundic-type epithelia.

In conclusion, these results show that patients with long segments of columnar-lined oesophagus or with specialized intestinal epithelium do not have more advanced gastro-oesophageal reflux disease, poorer oesophageal clearing or higher reflux rates. Therefore, from the point of view of gastro-oesophageal reflux disease they do not require a different therapeutic approach. However, since the degenerative potential of specialized intestinal epithelium is widely documented, endoscopic surveillance is required in these patients, whereas it still has to be determined in patients with gastric-type epithelium.

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Polymers that reduce intraperitoneal adhesion formation

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Background Viscous macromolecules and phospholipids have been shown to reduce postoperative adhesion formation. The ideal agent, or combination of agents, still remains to be identified.

Methods The effect of hydrophobically modified ethyl (hydroxyethyl) cellulose (HM-EHEC) and polyquarternium-24 (LM-200), two cellulose-derived polymers, and of sphingomyelin, was examined in an animal model. Adhesions were induced in the parietal peritoneum in a standardized manner and quantity, and the morphology of adhesion formation was evaluated after 7 days.

Results A significant reduction in adhesion formation was seen in animals receiving LM-200 ($P = 0{\cdot}013$) and HM-EHEC ($P = 0{\cdot}012$) as a short-term treatment compared with controls given saline, but not in animals receiving sphingomyelin ($P = 0{\cdot}733$). Additional effects were seen in the animals receiving LM-200 as a prolonged treatment ($P < 0{\cdot}001$) compared with controls. There was no difference in the magnitude of the inflammatory response between the groups.

Conclusion These results suggest that hydrophobically modified polymers are efficient in reducing adhesions, without affecting the inflammatory response.

Adhesion formation is a well known complication of abdominal and pelvic surgery, that not only renders reoperation more difficult but is also the most common cause of small bowel obstruction and mechanical infertility[1–3]. A recent survey showed that the annual medical expenditure for adhesive small bowel obstruction was almost £12 million[3]. Various methods and agents have been investigated to prevent adhesion formation, but as yet few have been proven to be effective.

The mesothelial cells of the peritoneum are covered with a film 5 μm thick. This thin layer contains significant concentrations of phospholipids, mainly phosphatidylcholine, phosphatidylethanolamine and sphingomyelin exerting surface activity[4]. The surfactants are easily destroyed by trauma, ischaemia and infection, which elicit phospholipases. In addition the light from surgical theatre lamps is known to induce lipid peroxidation, thereby interfering with phospholipid structure and function[5]. Exogenous phospholipids have been shown to reduce postoperative adhesions[6,7], possibly by providing a lubricant layer replacing endogenous hydrolysed phospholipid.

The ideal lipid, or combination of lipids and polymers, still remains to be identified. Cellulose consists of linear polymers of glucose residues. Binding of water leads to the formation of a gel. The hydrophobic modification of the surfactant polyquarternium-24 (LM-200) and hydrophobically modified ethyl (hydroxyethyl) cellulose (HM-EHEC), two cellulose-derived polymers, adds an affinity for the lipid–water interface likely to be at the injured site/cellular surfaces. Sphingomyelin has a structure similar to that of phosphoglycerides such as phosphatidylcholine but should, at least theoretically, be less susceptible to hydrolysis by lipases and phospholipases[8].

The precise mechanism of action of phospholipids and polymers is yet to be determined. In addition to their proposed mechanical function in separating and lubricating surfaces they are likely to have biological functions. Phospholipids are the substrate for arachidonic acid and sphingomyelin (95 per cent by weight), a major constituent of cell membranes. Cellulose-derived polymers are not endogenous and may therefore increase the inflammatory response.

The objectives of the present study were twofold; to test the primary hypothesis that sphingomyelin, HM-EHEC and LM-200 may reduce the formation of adhesions, and to investigate whether they affect the local inflammatory response or not.

Patients and methods

Animals

Some 154 female NMRI (US Naval Medical Research Institute) mice weighing 30–35 g were used. The experiments were approved by the local ethics committee. The animals had free access to pellets and water before and after surgery. They were allocated randomly to different experimental groups.

Compounds

Sphingomyelin (95 per cent by weight) was obtained from Swedish Dairy's Association, Research Department, Lund, Sweden. The sphingomyelin was diluted in sterile water to a final concentration of 1 per cent by weight. HM-EHEC (1 per cent by weight), a cationic polymer with five hydrophobic tails, was obtained from Akzo Nobel Surface Chemistry, Stenungsund, Sweden. LM-200 (1 per cent by weight) was obtained from Bionord, Gothenburg, Sweden. The compounds were kept refrigerated until used.

HM-EHEC is a soluble polymer that has been chemically modified to be hydrophobic, yet soluble in water. LM-200 is a polymeric ammonium salt of hydroxyethylcellulose, with a hydrophilic backbone and lipophilic pendant groups, which adds an affinity for the lipid–water interface. Solutions of hydrophobically modified polymers have been found to have higher viscosities than solutions of their unmodified analogues[9], a feature that may be of importance for mechanical separation of adjoining traumatized surfaces.

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Experimental design

One group ($n = 6$) underwent sham operation. Three groups were subjected to a short-term treatment and three groups were given a prolonged treatment.

The short-term treatment consisted of an intraperitoneal injection of either LM-200 ($n = 21$), HM-EHEC ($n = 21$) or sphingomyelin ($n = 16$) after closure of the abdominal cavity. Controls received saline ($n = 16$). The volume load was 0·75 ml (0·25 mg per g body-weight). The groups receiving prolonged treatment were given an intraperitoneal injection of either LM-200 ($n = 21$), HM-EHEC ($n = 21$) or sphingomyelin ($n = 16$), not only at the time of the operation but also on days 2 and 3 after operation. Controls received saline ($n = 16$). The volume load was the same on all three occasions (0·75 ml). Two animals from each group were killed on days 1, 3, 5 and 7 for morphological analysis of the tissue response.

Surgical technique

Anaesthesia was induced and maintained by inhalation of methoxyflurane. The abdomen was shaved and opened with a 2·5-cm midline incision. A 2 × 15 mm defect in the parietal peritoneum was created on each side of the lateral side wall by sharp incision along a metal ruler followed by excision with a pair of scissors. The lesion was closed with four 5/0 silk sutures, one at each end of the lesion and the other two at equal distance in between. The midline incision was closed in two layers by continuous 3/0 polyglycocolic mass closure (Dexon, Davis and Geck, St Louis, Missouri, USA). The procedure is described in detail elsewhere[10,11].

Evaluation

The objective was both to quantitate the formation of adhesions and to study the morphological response in the tissue. At days 1, 3 and 5 after operation, two animals from each group were killed by an overdose of isoflurane and biopsies were taken for morphological studies. Seven days after the operation the remaining animals were killed. The abdominal cavity was opened widely with a U-shaped incision with its base to the right of the animal. The flap was then turned over to the right so that the parietal peritoneum of the anterior abdominal wall and the adhesions attached to it were displayed. The lesions previously induced in the peritoneum were identified by the suture lines. The lengths of the original lesion and of the individual adhesion attachments were measured with a calliper. The percentage of the peritoneal defect that was covered with adhesions could then be calculated according to the formula: adhesions (%) = sum of attachments (mm)/excision site (mm) × 100 as described previously[10,11]. Besides quantification, the location and number of attachments were noted.

Morphology

The injured area was excised, including the parietal peritoneum, muscular layer and skin. The specimen was fixed in Bouin's solution for 24 h, dehydrated and embedded in paraffin wax. Sections were cut at a thickness of 5 μm and stained with haematoxylin and eosin.

Statistical analysis

Values are given as mean(s.e.m.). The non-parametric Mann–Whitney U test was used to determine the significance of differences in adhesion formation between groups. A P value less than 0·05 was considered statistically significant.

Results

None of the animals had adhesions at the beginning of the operation. All animals developed adhesions, except for two animals receiving LM-200 as a prolonged treatment. No animal developed bowel obstruction or displayed signs of general malaise.

Adhesion formation

The sham-operated group had no adhesions after operation, except at the midline incision. There was no significant difference in adhesion formation between the control group (69·0(4·5) per cent) and the group that was given sphingomyelin (69·7(6·7) per cent) ($P = 0·733$) as a short-term treatment (*Fig. 1*). The HM-EHEC-treated group had significantly less adhesion formation (48·1(5·1) per cent, $P = 0·012$) than the control, as did the group given LM-200 (44·2(6·3) per cent, $P = 0·013$). Repeating the injection of sphingomyelin 2 and 3 days after operation gave a reduction in adhesion formation (72·4(4·5) per cent, $P = 0·049$) compared with saline controls. Significantly fewer adhesions were seen in the groups receiving the long-term treatment with HM-EHEC (47·6(6·5) per cent, $P = 0·003$) or LM-200 (24·4(5·3) per cent, $P < 0·001$) compared with the control group given three injections of saline (84·5(6·2) per cent). There was no difference in effect between the group receiving HM-EHEC as a short-term treatment (48·1(5·1) per cent) and that receiving HM-EHEC as a prolonged treatment (47·6(6·5) per cent) ($P = 0·747$). The adhesion-reducing effect of LM-200 was significant with both the short- and long-term treatment but, in contrast to HM-EHEC, LM-200 was significantly more effective when given as a prolonged treatment (24·4(5·3) per cent) compared with the short-term treatment (44·2(6·3) per cent) ($P = 0·032$).

The number of adhesion attachments to different intra-abdominal structures (omentum/pelvic fat bodies (PFB); bowel; or other structures (predominantly liver)) was also

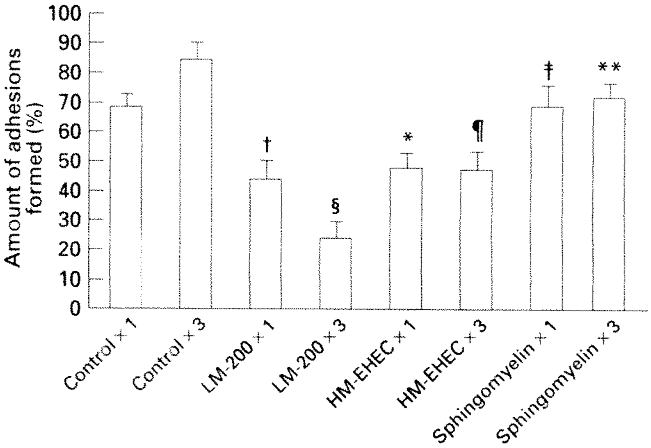

Fig. 1 Adhesion formation in animals subjected to different treatments. Values are mean(s.e.m.). Controls received saline as a single dose (control × 1) or for 3 consecutive days (control × 3). Treatment groups comprised animals receiving polyquarternium-24 (LM-200), hydrophobically modified ethyl (hydroxyethyl) cellulose (HM-EHEC) or sphingomyelin once (LM-200 × 1, HM-EHEC × 1 and sphingomyelin × 1) or three times (LM-200 × 3, HM-EHEC × 3 and sphingomyelin × 3). LM-200 and HM-EHEC were equally effective when administered once, but the performance of LM-200 was further improved by repeated administration. Sphingomyelin was less effective. *$P = 0·012$, †$P = 0·013$, ‡$P = 0·733$ *versus* control × 1, §$P < 0·001$, ¶$P = 0·003$, **$P = 0·049$ *versus* control × 3 (Mann–Whitney U test)

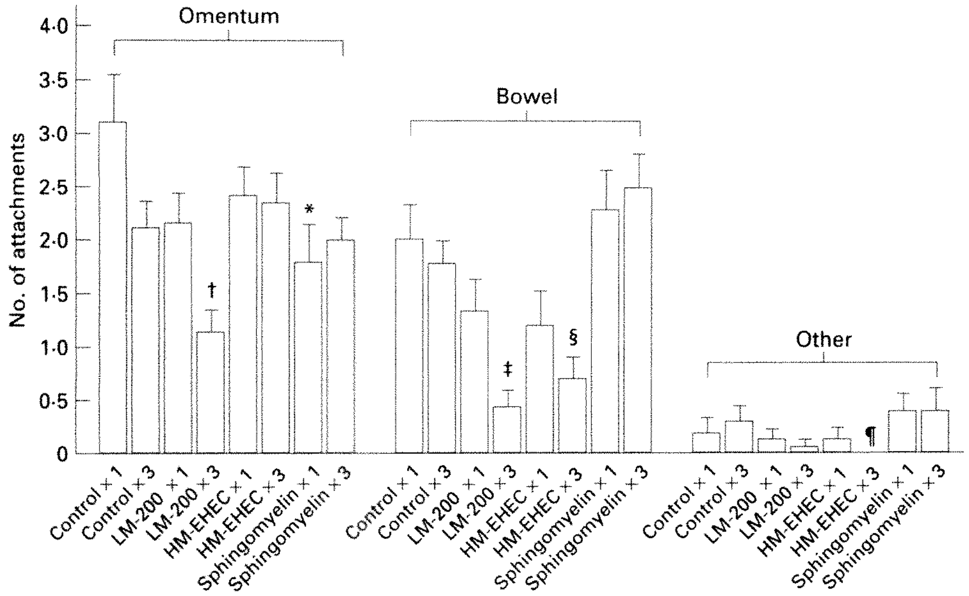

Fig. 2 Number of adhesion attachments to abdominal organs in animals subjected to different treatments. Values are mean(s.e.m.). A single administration (× 1) of polyquarternium-24 (LM-200), hydrophobically modified ethyl (hydroxyethyl) cellulose (HM-EHEC) or sphingomyelin did not significantly affect the number of attachments, whereas repeated administration (× 3) did in animals receiving LM-200 or HM-EHEC. $^*P = 0{\cdot}049$, $†P = 0{\cdot}023$, $‡P < 0{\cdot}001$, $§P = 0{\cdot}004$, $¶P = 0{\cdot}032$

studied (*Fig. 2*). LM-200 had no significant effect on the number of adhesions, given as a short-term treatment (PFB, $P = 0{\cdot}098$; bowel, $P = 0{\cdot}114$; other structures, $P = 0{\cdot}717$) compared with controls, nor did HM-EHEC (PFB, $P = 0{\cdot}205$; bowel, $P = 0{\cdot}103$; other, $P = 0{\cdot}717$). Sphingomyelin reduced the number of attachments to omental structures, but not to bowel and other parts of the abdominal cavity (PFB, $P = 0{\cdot}049$; bowel, $P = 0{\cdot}434$; other, $P = 0{\cdot}342$).

LM-200 given in three consecutive doses gave a significantly reduced number of attachments to both omentum ($P = 0{\cdot}023$) and bowel ($P < 0{\cdot}001$) but not to other structures ($P = 0{\cdot}147$). HM-EHEC reduced the number of attachments to bowel ($P = 0{\cdot}004$) and other structures ($P = 0{\cdot}032$) but not to omentum/PFB ($P = 0{\cdot}596$). Given as a long-term treatment, sphingomyelin had no effect on the number of attachments to any of the structures involved (PFB, $P = 0{\cdot}720$; bowel, $P = 0{\cdot}091$; other, $P = 0{\cdot}888$). Prolonged LM-200 treatment gave significantly fewer adhesions to both omentum/PFB ($P = 0{\cdot}023$) and to bowel ($P = 0{\cdot}032$) compared with the group that received the short-term treatment, but not to other structures ($P = 0{\cdot}549$).

Tissue response

An inflammatory reaction was seen at the site of adhesion formation, not only at the attachment site and in the abdominal wall, but also in the adherent non-injured tissue. On day 1 after surgery polymorphonuclear neutrophils dominated and later macrophages were abundant. A uniform morphological appearance was seen on specimens obtained from all groups, and there was no difference between the treatment groups and the control group. Furthermore, there was no difference between the groups given short-term and long-term treatment.

Discussion

In this study hydrophobically modified polymers such as LM-200 and HM-EHEC significantly reduced the amount of postoperative adhesion formation in an experimental model and prolonging the treatment of LM-200 reduced the number of attachments as well as the amount of adhesions. Sphingomyelin, which is structurally related to phosphatidylcholine, had beneficial effects on the amount of adhesions only when given repeatedly, but reduced the number of attachments to omentum in the short-term group.

The experimental model was chosen because it is a strictly standardized quantitative model mimicking abdominal surgery and has previously been shown to be reproducible with a low variability in the amount of adhesions formed[10,11]. Furthermore, the model enables the study of adhesion formation from two different perspectives: the amount of adhesions covering a standardized lesion and the number of attachments to the lesion and organs involved. It seems reasonable to assume that the amount of adhesions covering a standardized lesion accurately reflects the adhesiogenic stimuli to that site and that the organs involved are of importance, but the significance of the number of attachments remains to be validated. Nevertheless, there was fairly good agreement between the amount of adhesions formed and the number of attachments indicating that they represent the same thing. Mice were used, not only because they are cheap and practical to work with but also because in this model they have a relatively high frequency of involvement of non-injured bowel compared with other species[11]. From a clinical point of view this was considered an advantage, since complications often arise from adhesions involving the bowel.

The kinetics of degradation and absorption of sphingomyelin, LM-200 and HM-EHEC in the abdominal cavity are unknown so both short- and long-term treatments were studied. Furthermore, since the mechanism of action was unclear, the duration of administration required was uncertain. Physical barriers have been demonstrated to effectively reduce the formation of adhesions if they separate surfaces for at least 36 h[12], and therefore a 3-day treatment was believed to be sufficient.

Previously, soluble phosphatidylcholine has been shown to reduce postoperative adhesions[13], whereas insoluble phosphatidylcholine liposomes had the opposite effect[14]. Sphingomyelin forms liposomes in analogy to related saturated phosphatidylcholine systems[8]. In the case of phosphatidylcholine liposomes, impaired macrophage function and reduced lymphatic absorption due to enhanced net ultrafiltration was considered to be involved in the adhesion promoting effect. This might partly explain why sphingomyelin was less efficient than the other agents in reducing adhesion formation.

Plasminogen activator plays a crucial role in fibrinolysis, which is suppressed by surgical manipulation[15,16] and is pivotal in adhesion formation[17]. Mayer and co-workers[18] investigated the effect of dextran and other viscous polymers on peritoneal plasminogen activator activity and showed that the polymers investigated reversibly suppressed tissue-bound plasminogen activator and impaired the secretion of peritoneal plasminogen activator activity. This suggests a possible mechanism of action for polymer coating in reducing adhesion formation by impairing the shedding of the enzyme, thereby producing a high local concentration of plasminogen activator activity on peritoneal surfaces.

A steric–osmoic antiadhesive effect is probably one important mechanism of action of these substances. In forming a film covering the injured peritoneum they keep intra-abdominal structures from coming into continuous, close apposition by fibrin, thereby preventing adhesions from forming. This may be accomplished if the polymers inhibited the attachment of fibrin. Another possibility is that these polymers modify the polymerization or cross-linking of fibrin monomers, thereby reducing the 'stickiness' of deposited fibrin.

The reason for the increased efficacy of LM-200 but not of HM-EHEC, when given in three consecutive doses, may be attributable to electrostatic interactions. LM-200, being positively charged, will have a tendency to associate with negatively charged surfaces. However, it may also indicate that their biological effects and mechanism of action are different. None of the compounds investigated affected the inflammatory response as judged from the amount of cells present, but the functional characteristics of the cells were not investigated and may have been different between LM-200 and HM-EHEC groups.

The cellulose-derived polymers investigated were efficacious in reducing the formation of adhesions without affecting the inflammatory response and one of them was more effective if given repeatedly. The mechanism of action remains unclear, but there may be multiple actions including the separation of surfaces, increasing the local tissue plasminogen activator levels and altering the adhesive properties of fibrin. Two cellulose-derived membranes are currently approved for clinical use (Interceed, Johnson and Johnson, New Brunswick, New Jersey, USA; Seprafilm, Genzyme, Cambridge, Massachusetts, USA). However, the safety of polymers used in the present study requires further investigation before being applied in clinical practice.

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The Editors welcome topical correspondence from readers relating to articles published in the Journal. Letters should be no more than 250 words in length and should be typed on A4-sized paper in double-spacing.

Pathological appearance of the stomach after endoscopic mucosal resection for early gastric cancer

Sir

We read with interest the findings presented by Korenaga *et al.* (*Br J Surg* 1997; **84**: 1563–6) regarding endoscopic mucosal resection (EMR) of gastric cancer. There is no doubt that EMR plays an important rôle in the management of this disease, especially in Japan where extensive experience has been gained. This study, however, appeared to disregard essential criteria for the selection of patients for EMR established by Sano *et al.*[1] over 5 years ago which allowed selection of a subgroup of patients with early gastric cancer with minimal risk of lymph node metastasis where endoscopic treatment would not compromise the curative intent.

Disease confined to the mucosa is the most important of the established criteria and yet six of 11 tumours had submucosal spread. Lesions greater than 15 mm in diameter are not suitable for EMR but were included in this study resulting in incomplete excision. Finally type IIc tumours with ulceration were included in this study and lymph node metastases were found in some of these patients.

The authors do not make clear the reasons for subsequent surgery. For example, why did some patients with recurrent disease proceed to further EMR while others with positive resection margins proceeded to surgery? What was the protocol regarding management of these patients?

This paper has highlighted some of the pitfalls in the use of EMR for gastric cancer and confirmed the importance of limiting its use to those who fulfil carefully established criteria and in whom EMR will not compromise potential cure. The finding of lymph node metastases in patients treated endoscopically is unacceptable.

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1 Sano T, Kobori O, Muto T. Lymph node metastases from early gastric cancer: endoscopic resection of tumour. *Br J Surg* 1992; **79**: 241–4.

Author's reply

Sir

We thank Kundu *et al.* for their constructive comments. Of course, cure is a mandatory goal for the treatment of early gastric cancer. In earlier years, EMR remained a challenge. From this retrospective analysis we found that accurate diagnosis of width and depth of invasion must be assessed before EMR. Improvements in recent years may be a result of the use of endoscopic ultrasonography before EMR to assess the depth of invasion and the application of electrocautery to destroy cancer cells around the resected margin.

Assessment of the depth of invasion from an endoscopically resected specimen is important in making therapeutic decisions. The present policy is to perform subsequent surgery when (1) there is infiltration of cancer cells in the submucosal layer, or (2) lymphatic or vascular invasion is observed. If malignant cells are likely to remain in the mucosa around the resected margin but the submucosal layer is not invaded, repeated EMR is the treatment of choice. Our paper confirmed that understanding the indications and limitations of EMR is necessary. We agree that EMR should be indicated for carefully selected patients with early gastric cancer with minimal risk of lymph node metastases.

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Hereditary breast cancer

Reply to letter published in previous issue (*Br J Surg* 1998; 85: 570–1)

Sir

We would like to thank Hicken *et al.* for the interest they have shown in our Review (*Br J Surg* 1997; **84**: 1334–9). We acknowledge that we did not provide strict guidelines on the management of these patients because our understanding in this area is rapidly evolving and remains controversial.

As an example, Hicken *et al.* correctly quote our review saying that the lifetime risk for carriers of *BRCA1* mutations is 50–60 per cent. Since publication of the Review, this fact is now disputed by a recent large study suggesting that the lifetime risk for *BRCA1* carriers of developing ovarian cancer is closer to 16 per cent[1].

Hicken *et al.* make a reasonable suggestion for performing laparoscopic oophorectomy as adjuvant therapy for patients with *BRCA1*-associated cancer and suggest that this should be performed for those with *BRCA2*-associated breast cancer. The latter would not reduce any potential risk of developing ovarian cancer as *BRCA2*-mutations are not associated with an increased risk of developing ovarian cancer.

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1 Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M *et al.* The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. *N Engl J Med* 1997; **336**: 1401–8.

Effect of a no-conversion policy on patient outcome following laparoscopic cholecystectomy

Sir

We share the concerns expressed by Wallace and O'Dwyer (*Br J Surg* 1997; **84**: 1680–2) on the potential lack of experience of open cholecystectomy by surgical trainees in the laparoscopic era. We feel that their paper did not adequately address this issue.

The not insignificant number of open cholecystectomies performed during the no-conversion period and the admirably short time taken for trainees to perform the laparoscopic procedure attest to a successful case selection policy in this unit. The reasons for conversion to an open procedure before adoption of the no-conversion policy included haemorrhage and failure to define anatomy. Are the authors suggesting that the surgeon should always persist with the laparoscopic procedure in the face of such difficulties? We find it particularly difficult to justify their conclusion that the inexperienced surgeon should consider laparoscopic subtotal cholecystectomy or cholecystostomy with stone removal in preference to open cholecystectomy when the one such patient in their series required an open operation at 48 h for major complications with this approach.

Conversion to an open procedure in difficult cases is justified and attention should thus focus on the adequate training of surgical trainees in surgical procedures that will enable them to cope adequately.

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Author's reply

Sir

I am sure that Garden *et al.* would agree that the reasons for conversion (haemorrhage and failure to define anatomy) occur less frequently as experience is gained with laparoscopic cholecystectomy. I am also sure that even they may need to revert to cholecystostomy or subtotal cholecystectomy for the occasional gallbladder that resists both laparoscopic and open cholecystectomy.

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Correlation between blood loss and inferior vena caval pressure during liver resection

Sir

We read with interest the paper by Johnson *et al.* (*Br J Surg* 1998; 85: 188–90) reporting that the higher the inferior vena cava (IVC) pressure, the greater the venous engorgement of the liver which leads to increased blood loss during liver resection.

There are three points of concern. First, the authors did not mention whether there was any correlation between IVC pressure and superior vena caval pressure, the latter of which is usually monitored as the central venous pressure during liver resection. Second, IVC pressure was measured only at certain time points instead of continuously. Surgical manipulation of the liver may distort the IVC. IVC pressure will fluctuate during liver transection and therefore simply measuring at several time points for the calculation of mean pressure may introduce unreliable results. In a similar study we measured the venous pressure continuously and calculated the mean pressure by measuring the 'area under the curve' on a plot of pressure against time. This method gives a more precise and accurate measurement of the venous pressure throughout the period of liver transection. Third, the authors described four patients with a high caval pressure who developed postoperative complications. Significant amounts of blood can be lost during mobilization of the liver, especially if cirrhotic, requiring aggressive intravenous infusion of fluid which may lead to higher caval pressure before liver transection. Normally patients who lose more blood during operation are more likely to encounter postoperative complications. Therefore, total blood loss for the entire operation as well as the blood loss during liver transection should be examined for a correlation with the morbidity following hepatectomy.

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Dynamic graciloplasty for severe anal incontinence

Sir

The series of patients treated with an electrostimulated gracilis neosphincter and reported by Christiansen *et al.* (*Br J Surg* 1998; **85**: 88–91) conforms to the experiences of ourselves and others[1–3] who have encountered a number of complications, including rectal evacuatory disorders, associated with this procedure. Although the authors showed an apparent improvement in continence scores in the majority of cases, nine of the 13 patients described required revisional surgery, and three of the 13 had a poor outcome because of rectal evacuatory difficulties.

Inevitably, the use of any current continence grading scale alone is only a partial measure of outcome because it fails to assess complications and new symptoms, such as pain or constipation, that the patient may suffer after graciloplasty. Such patients may have improvements in continence, but still encounter a deterioration in overall quality of life as a result of surgery. While the visual analogue scale used by the authors allowed the patients retrospectively to report their opinion of surgical outcome, we assume that in this report continence and patient satisfaction were assessed by the surgical team treating the patient, a situation that may lead to a number of potential biases[4].

For these reasons we believe it is preferable to submit novel procedures such as the electrically stimulated gracilis neosphincter to an independent global quality-of-life evaluation using confidential questionnaires. This allows the patients to indicate whether their symptoms and lifestyle have changed after surgery to a researcher who is not part of the surgical team. Accordingly, an independently funded and managed prospective comparative trial of quality of life and cost utility of the gracilis neosphincter has now been set up at our institution[5]. We would commend this approach to all colleagues seeking objectively to evaluate the results of surgery for any new surgical procedure.

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1 Mander BJ, Abercrombie JF, George BD, Williams NS. The electrically stimulated gracilis neosphincter incorporated as part of total anorectal reconstruction after abdominoperineal excision of the rectum. *Ann Surg* 1996; **224**: 702–11.
2 Wexner SD, Gonsalez-Padron A, Rius J, Teoh TA, Cheong DM, Nogueras JJ *et al.* Stimulated gracilis neosphincter operation: initial experience, pitfalls and complications. *Dis Colon Rectum* 1996; **39**: 957–64.
3 Geerdes BP, Heineman E, Konsten J, Soeters PB, Baeten CGMI. Dynamic graciloplasty: complications and their management. *Dis Colon Rectum* 1996; **39**: 912–17.

4 O'Boyle CA. Assessment of quality of life in surgery. *Br J Surg* 1992; **79**: 395–8.
5 Jack D. Avoiding stomas with total anorectal reconstruction. *Lancet* 1997; **349**: 1750.

Authors' reply

Sir
We agree that a more precise description of the role of defaecatory disorders in assessment of quality of life is an important issue when treating patients with anal incontinence.

We have demonstrated that dynamic graciloplasty carries the risk of a number of different side-effects. Unexplained impaired rectal evacuation is one of the most disturbing.

As treatment for anal incontinence should improve quality of life, assessment of quality of life before surgery will, in the future, be mandatory. Until now, quality-of-life scales have not been able to place defaecatory disorders in a meaningful context for the total assessment of quality of life.

We, therefore, welcome the initiative of Eccersley and Williams to set up a prospective trial of quality of life in relation to the gracilis neosphincter procedure evaluated by independent researchers. Hopefully the quality-of-life questionnaire that the authors mention will be made available to surgeons outside the UK.

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'Routine' pathological examination of the gallbladder is a futile exercise

Letter 1

Sir
The paper by Taylor and Huang (*Br J Surg* 1998; **85**: 208) was interesting and controversial. Although it makes minor economic sense, their suggestion that the practice be abandoned in favour of a 'more considered approach' relied on only six cancers correctly and intuitively suspected by the (presumably different) operating surgeons. Perhaps the same surgeons may not have done so well with 1045 early cancers. To discard 70 per cent of specimens to save £1000 plus 25 consultant-hours per year would seem trifling compared with the cost and anxiety of missing one early cancer. In an ongoing questionnaire study at this institution the details of port-site recurrences are collected. There have been surprise retrospective histological diagnoses of which the surgeons had no preoperative or peroperative intimation. Preoperative diagnosis of early gallbladder cancer is notoriously difficult and, if this cannot be confidently distinguished from chronic inflammation (97 per cent of the authors' specimens) or even dysplasia macroscopically, then histology remains mandatory. With reports of laparoscopic dissemination of *in situ* carcinomas[1] and some long-term survival[2], it is prudent not to miss such a diagnosis, rare though this will be. We would like to know whether the authors have changed their practice (or policy) in the light of their findings.

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1 Wibbenmeyer LA, Wade TP, Chen RC *et al.* Laparoscopic cholecystectomy can disseminate *in-situ* carcinoma of the gallbladder. *J Am Coll Surg* 1995; **181**: 504–10.
2 Bartlett DL, Fong Y, Fortner FG, Brennan MF, Blumgart LH. Long term results after resection for gallbladder cancer. *Ann Surg* 1996; **224**: 639–46.

Letter 2

Sir
Taylor and Huang conclude their paper by saying that the routine histological examination of all excised gallbladders should be abandoned and a 'more considered approach adopted'. The key phrase is the last one, which could be extended much more widely within medical practice generally. As far as pathology in general is concerned, I suspect that many tests and investigations are requested for no particularly good reason and that the results do not have any significant effect on patient management. The important question that should always be asked by clinicians is 'How will the results of this test affect the management of this patient?'. If they cannot think of a reasonable answer, then arguably the test should not be requested. Tests to exclude conditions may, of course, be as valuable as those that support a diagnosis.

An increasing histopathological workload, in terms of numbers and complexity of assessment, is causing serious problems, requiring radical solutions[1]. My colleagues and I have recently suggested that the Royal College of Pathologists should examine the problem of specimens that need not be sent for histopathological examination or, if sent, require no more than macroscopic assessment[2]. Such an exercise would require wide consultation, not least with other royal colleges that should have an important role in this process. Similar considerations could, of course, be extended more widely (e.g. biochemical and radiological tests). I do hope that surgeons take up the challenge implicit in Taylor and Huang's paper and assess critically the use of clinical support services. As things stand there is a danger that the quality of work will be affected adversely by its volume, a significant part of which I believe to be unnecessary for directing patient management.

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2 Ball RY, Barker THW, Girling AC, McCann BG, Sams VR, Tyler XT. A hitchhiker's guide to survival. *Bulletin of the Royal College of Pathologists* 1998; **103** (Letter) (in press).

Letter 3

Sir
We read with interest the article by Taylor and Huang. The assertion that most gallbladder specimens need not be subjected to histological examination is in opposition to standard surgical teaching. We do not consider this strategy to be viable in the current medicolegal climate, with litigation cases increasing by 15 per cent per annum in the UK[1]. The authors would have to defend their policy in the context of a missed gallbladder cancer. Litigation cases where the medical records are found to be inadequate usually find in favour of the plaintiff. It would be difficult to prove that the gallbladder resection margins from a patient with unrecognized cancer were tumour-free, if no specimen was available for histological confirmation. In a review of

338 patients with cancer, in whom there had been a delay in diagnosis, Kern[2] identified two factors that made litigation more likely: cancers occurring in young and middle-aged patients and cancers associated with high cancer-specific mortality. A typical cholecystectomy patient would fall within this age group.

The desire to reduce expenditure is admirable but we think the authors are brave to implement such a policy.

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1 Tomkins C. Tough defence for our members. *Journal of the Medical Defence Union* 1998; **14**: 1.
2 Kern KA. Medicolegal analysis of the delayed diagnosis of cancer in 338 cases in the United States. *Arch Surg* 1994; **129**: 397–404.

Authors' reply

Sir

We agree with Zayyan and Sellu, and Bowrey *et al.*, that cost should not be of primary concern here but repeat that, based on current evidence, dysplasia and early cancers (i.e. *in situ* and T_1 tumours) require only simple cholecystectomy.

Both papers quoted by Zayyan and Sellu confirm this view. We have found no data to suggest that excision of port sites after uncovering a T_1 tumour affects outcome. The accurate distinction between these early conditions macroscopically and microscopically does not, therefore, alter the management of the patient.

In Zayyan and Sellu's study, it is unclear what is meant by 'surprise retrospective diagnoses'. Was cancer not diagnosed at the initial histological examination and only when re-examined after recurrence was found? If so, what was the value of the pathologist's involvement and should all specimens be kept so that, if port-site recurrence is found, the diagnosis can be confirmed merely for surgeon satisfaction, with no change in patient management?

When a routine specimen arrives at the pathology laboratory it is examined macroscopically by a pathologist, often a trainee, and standard sections are taken from the fundus and neck (not the surgical margin). Further sections will be cut only if there is a suspicious area. Surgical trainees and consultants might be trained to the same standard as a pathology trainee in recognizing macroscopic abnormalities of the gallbladder.

Medicolegally a surgeon would not be deemed negligent if any action were accepted by a responsible body of medical opinion (Bolam principle). If the Royal Colleges of Surgeons and Pathologists could agree on guidelines and a protocol, then surely the courts would be satisfied?

We recommend that careful inspection of the gallbladder should be carried out after excision and must include opening the specimen to examine the mucosa. Surgeons should record operative findings in greater detail and be familiar with features that merit formal histological examination: (1) discrete lesion (e.g. polyps, irregular nodules or ulcerated areas), and (2) diffuse infiltration (e.g. firm, thickened and indurated wall with gritty consistency, or penetration into the liver bed, or spread to the porta hepatis lymph nodes).

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Activated protein C resistance: the commonest hereditary hypercoagulation disorder

Letter 1

Sir

We read with interest the leading article by Schuster and Jentschura (*Br J Surg* 1997; **84**: 1633–5) of a patient with activated protein C (APC) resistance who presented at an advanced age with mesenteric venous thrombosis. We had a similar experience with a 54-year-old man whose first presentation was with mesenteric venous thrombosis requiring small bowel resection and anastomosis. Subsequent thrombophilia screening showed him to be homozygous for factor V Leiden (APC resistance). Our patient has a strong family history of thrombosis with his late mother, two aunts and a sister all having had recurrent episodes of deep vein thrombosis.

Previously reported studies[1–5] suggest that between 9 and 62 per cent of cases of primary mesenteric venous thrombosis have no underlying cause found. With the discovery of APC resistance as the commonest hereditary coagulation disorder, the incidence of idiopathic mesenteric venous thrombosis should be much lower in future. We suggest that with screening of the relations of those with APC resistance, and prophylatic anticoagulation of those affected, there should be a reduction in the incidence of this condition.

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Letter 2

Sir

We enjoyed the leading article by Schuster and Jentschura. Our comments concern the association of factor V Leiden with 'venous' leg ulceration. Chronic venous insufficiency leading to 'venous' leg ulcers is a significant medical problem. The prevalence of leg ulcers in one study of 92 100 subjects aged over 40 years was 0·38 per cent[1]. Up to 72 per cent of patients with leg ulcers have detectable venous insufficiency[2]. In more than 50 per cent of all leg ulcers venous insufficiency is either the sole or the predominant cause.

Factor V mutations are now known to be responsible for a higher proportion of deep venous thrombosis (DVT) cases than previously thought[2,3]. Many affected patients would progress to venous insufficiency and ulceration. In 70–90 per cent of cases the activated protein C resistance (APCR) phenotype is caused by a single nucleotide change of guanine to adenine at position 1691 of the factor V gene[4,5]. Factor V Leiden[4] and associated APCR have been found in about one-quarter of all patients with venous leg ulcers.

We sugest that venous ulceration is a reason for suspecting APCR due to variant factor V. Affected patients are candidates for recurrent thrombosis and progressive disease[6]. Their relatives have a higher susceptibility than normal as well. The presence of venous ulceration, even without any history of DVT, should be added to the possible indications for screening for factor V Leiden. Similarly, studies are required to establish whether selected patients would benefit from preventive therapy to avoid further deterioration of the venous condition. This could potentially help in healing ulcers and prevent recurrences.

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2 Nelzen O, Bergqvist D, Lindhagen A. Leg ulcer etiology – a cross sectional population study. *J Vasc Surg* 1991; **14**: 557–64.
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5 Munkvad S, Jorgensen M. Resistance to activated protein C: a common anticoagulant deficiency in patients with venous leg ulceration. *Br J Dermatol* 1996; **134**: 296–8.
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Authors' reply

Sir

We appreciate the comments from Khogali and colleagues regarding the similar findings of APC resistance in a patient with mesenteric vein thrombosis. As noted in our article we propose screening measures for patients who present with an unusual location of thrombosis.

An interesting aspect is raised by Sulaiman-Shoab concerning venous leg ulceration and APC resistance. DVT remains an important cause of venous leg ulcers but can be masked by the diagnosis of chronic venous insufficiency. We agree that additional studies are required to protect the patient with venous leg ulcers from further problems due to APC resistance. In addition to prophylactic anticoagulant therapy special attention should be directed towards the offspring of these patients. Hopefully, cost-effective screening of patients and relatives will be available in the near future. The incidence of idiopathic causes of venous thrombosis is likely to decrease further as the detection of APC resistance becomes part of the daily laboratory routine.

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Laparoscopic stoma formation for faecal diversion

Sir

We read with interest the article by Hollyoak *et al.* (*Br J Surg* 1998; **85**: 226–8) reporting the results of a study comparing laparoscopic and open techniques of stoma formation to defunction diseased colon. Fifty-five patients underwent either laparoscopic mobilization of a bowel loop before stoma formation or a midline laparotomy to mobilize an appropriate loop. The method of patient selection was not stated. The authors failed to mention a technique that is simpler, quicker and more commonly used: the fashioning of a loop or end colostomy via a small transverse incision at the desired site[1]. The bowel can usually be exteriorized without need for mobilization and a colostomy formed. This obviates the need for a laparotomy or the use of a pneumoperitoneum, thereby reducing pain, operating time and morbidity.

We accept that, when there are adhesions from previous surgery or widespread intraperitoneal disease, identification and mobilization of an appropriate loop may not be possible. Only in this minority of patients is a laparotomy or a laparoscopic approach required. As most defunctioning colostomies can be effected without a laparotomy, it would have been more appropriate to have compared laparoscopic colostomy formation with stoma formation through a small transverse incision. This study seems to represent a rather overzealous application of new technology.

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Author's reply

Sir

We thank Marshall and McPartlin for their comments and agree that the use of a single transverse incision to create a transverse colostomy is the method of choice for this particular stoma, but believe that a transverse colostomy is an inferior stoma. It is sited in the upper abdomen, defunctions poorly if brought out as a loop and has the propensity to prolapse. The ileostomy or sigmoid colostomy are preferred stomas.

In the thin patient with no adhesions it may be possible to identify and exteriorize the terminal ileum via a small trephine. According to anecdotes, the proximal and distal limbs may be confused and the distal limb becomes spouted. A laparoscopic approach enables quick and certain identification and prevents this problem.

With a sigmoid colostomy it is hard to believe that the sigmoid can be safely brought out through the anterior abdominal wall without mobilization of the lateral peritoneal reflection. This can be performed through a limited transverse incision over the stoma site but this incision is somewhat large. In most of our patients a laparoscopic mobilization was straightforward to perform (even in the presence of adhesions) and the only incision over the stoma site was for the trephine. Furthermore, if a stoma is brought out through a transverse incision, the skin trephine is not circular and angulation of the mucocutaneous junction results. This leads to skin furrowing which makes sealing of appliances more difficult, especially in overweight patients.

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Lateral rectal ligaments contain important nerves

Sir

We endorse the presence of the lateral ligament demonstrated by Rutegård *et al.* (*Br J Surg* 1997; **84**: 1544–5). The lateral ligaments are closely inter-related to the pelvic plexus which is a fenestrated rectangular plate of sympathetic and parasympathetic fibres (*Fig. 1*). This provides innervation to the bladder, ureter, prostate, seminal vesicles, membranous urethra and corpora cavernosa via anterolateral branches, and to the distal rectum via medial branches[1]. Conceivably, the nerve fibres elegantly illustrated by the authors by immunohistochemistry were the rectal branches of the pelvic plexus. It is only the medial segment of the lateral ligament that is included in the resection during rectal cancer surgery[2]. Before sharp dissection of the lateral ligament we routinely find the location of the plexus by tracing the exposed hypogastric nerve or direct palpation. The pelvic plexus is, therefore, rarely injured during the division of the lateral ligament. Partial injury of the pelvic plexus results in temporary loss of genitourinary function.

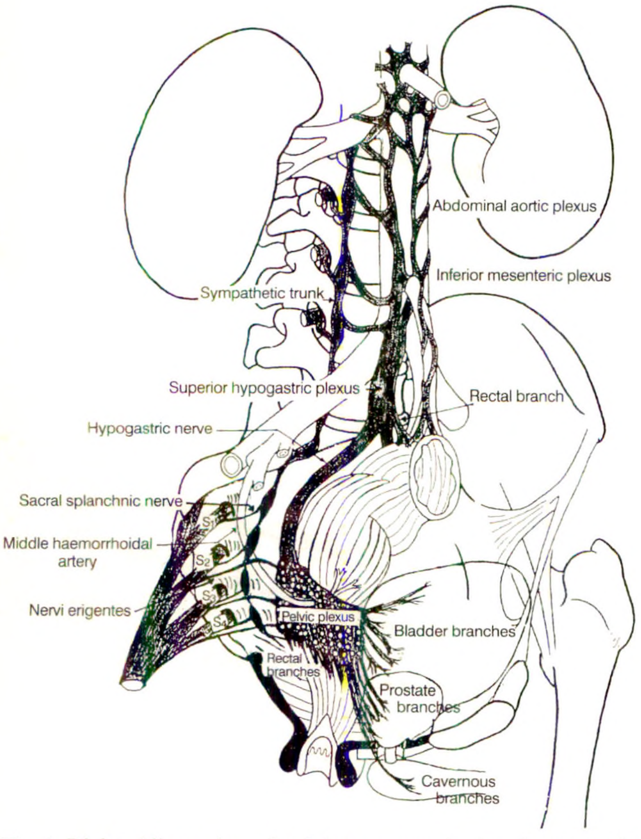

Fig. 1 Right oblique view of pelvic organs and related autonomic neuroanatomy

The periprostatic plexus represents a further challenge for colorectal surgeons endeavouring to perform autonomic nerve-preserving lower rectal cancer surgery. The periprostate plexus, running between the anterolateral rectal wall and the prostate, is vulnerable to inadvertent dissection which results in sexual dysfunction[3].

Whether the middle rectal artery is included in the lateral ligament or not is of little clinical significance because its small size allows easy control by cautery.

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1 Nivatvongs S, Gordon PH. Surgical anatomy. In: Gordon PH, Nivatvongs S, eds. *Principles and Practice of Surgery for the Colon, Rectum and Anus.* St Louis, Missouri: Quality Medical Publishing, 1992: 31–6.
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3 Weinstein M, Roberts M. Sexual potency following surgery for rectal carcinoma. *Ann Surg* 1977; **185**: 295–300.

Authors' reply

Sir

We appreciate the comments from Liang *et al.* and agree with their description of the nerve anatomy. Their illustration has the advantage of clearly showing the sympathetic trunk which can often be visualized even in the presacral area but may give rise to the misunderstanding that the hypogastric nerves and the pelvic plexuses lie close to the rectal wall; in fact they can usually be found on the pelvic side wall.

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Perioperative allogeneic blood transfusion does not cause adverse sequelae in patients with cancer: a meta-analysis of unconfounded studies

Letter 1

Sir

May I be allowed to comment on the apparent disregard of scientific objectivity and use of inappropriate methodology by McAlister *et al.* (*Br J Surg* 1998; **85**: 171–8). The authors found six randomized trials and two prospective cohort studies eligible for a meta-analysis investigating perioperative allogeneic blood transfusion and adverse sequelae in patients with cancer. Their conclusion, that there is no increased risk of clinically important adverse sequelae, cannot be drawn from the analysis.

The six randomized trials are graded from 1 to 3 on the Jadad scale. In another meta-analysis[1] five of the same six studies were categorized as level 1 (strong convincing data from large randomized trials). There is, however, discrepancy in the methodology, presentation of results and conclusion of the present meta-analysis. First, the authors claim that allogeneic blood transfusion does not increase the risk of postoperative infectious complications. This conclusion cannot be drawn as all the included studies separately demonstrated a significant increased rate of infectious complications in such patients compared with comparable non-transfused patients.

Instead, the discrepancy between the studies was whether the use of autologous or leucocyte-depleted blood could minimize this difference. The authors stressed that the elected trials using autologous blood transfusion or leucocyte-depleted packed cells acted as the control arm. This is true but they did not discuss the important aspect of the analysis where two different immunogenic transfusions are used. Furthermore, in their presentation of results (for example, *Table 4*) they confused patients being transfused with control blood and non-transfused patients as well as mixing infectious complications in different ways (for example, in some of the studies they included pneumonia and in others they did not).

In the investigation of results the authors found a summary risk ratio of 1·63 for postoperative infections, suggesting an increased risk. They then excluded two of the studies, claiming them to be heterogeneous and concluded that the risk factor was 1·0, indicating no risk.

The two excluded trials[2,3] were prospective randomized trials of patients undergoing colorectal surgery and randomized to receive leucocyte-depleted or non-depleted blood if transfusion was indicated. Patients with differing diagnoses were evenly distributed between the two transfused groups. It did not matter, therefore, that fewer patients had rectal cancer than in other trials.

McAlister *et al.* made major criticisms of the excluded studies for not transfusing control patients with allogeneic blood, whereas in other trials '10–35 per cent of control patients received crossover blood products'. This criticism is unfair as in the Jensen trials the control patients, according to the terminology of McAlister *et al.*, received leucocyte-depleted blood (which is also allogeneic) and the 'treatment' group received blood with leucocytes, i.e. blood with potentially immunosuppressive effects. The fact that only 1 per cent of control patients received crossover blood products is not a criterion for heterogeneity or exclusion. It means that only 1 per cent of patients received the inappropriately randomized blood product (compared with 10–35 per cent of patients in the other trials).

This meta-analysis does not, therefore, contribute further clarification concerning the adverse effects of blood transfusion.

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1 Blajchman MA. Allogeneic blood transfusion, immunomodulation, and postoperative bacterial infection: do we have the answers yet? *Transfusion* 1997; **37**: 121–5.
2 Jensen LS, Kisameyer-Nielsen P, Wolff B, Qvist N. Randomised comparison of leucocyte-depleted *versus* buffy-coat-depleted blood transfusion and complications after colorectal surgery. *Lancet* 1996; **348**: 841–5.
3 Jensen LS, Andersen AJ, Christiansen PM. Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. *Br J Surg* 1992; **79**: 513–16.

Letter 2

Sir

A distinguished critic of meta-analysis, John Bailar, has written that meta-analysis is characterized by '. . . the false appearance of objectivity but consistent bias in the studies selected for analysis, heterogeneity in the effects compared . . . and lack of sufficient knowledge on the part of the meta-analyst to interpret results correctly . . .'[1]. In an article giving evidence for each of these points, McAlister *et al.* conclude 'there is no evidence that allogeneic blood transfusion increases the risk of clinically important adverse sequelae in patients with cancer undergoing surgery.'

The authors exclude a randomized trial in patients undergoing cardiac surgery demonstrating that leucocyte-depleted blood reduces postoperative infection rates substantially and postoperative mortality by more than twofold, for the scientifically indefensible reason that it does not involve cancer patients[2,3]. They proceed further to exclude from their final risk estimates two of the strongest studies that contradict their conclusions, using arbitrary mathematical criteria for this decision[6,8]. This enables them to achieve a statistically non-significant risk ratio. The authors, therefore, reach their conclusions only after dismissing three[3–5] of the six extant randomized studies of transfusion immunomodulation. Perhaps coincidentally, all three studies eliminated contradict the conclusions of McAlister *et al.* Excluding these studies, they none the less choose to combine in their analysis studies with treatment arms of either autologous transfusion[6,7] or leucocyte-depleted transfusions[4,5,8]. These treatments are not immunologically[9] or clinically equivalent. Such results should not be pooled without further analysis in this manner.

Finally, it may be worth pointing out that generally accepted criteria for evaluating causality include (1) epidemiological evidence, (2) animal model data, (3) mechanistic studies and (4) randomized controlled trials. As the authors meaningfully discuss only the last of these subjects, and that with dismissal of half of the available data, the issue of causality cannot be even remotely addressed by their meta-analysis.

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1 Bailar JC III. Assessing assessments. *How Science Takes Stock.* Hunt M. *Science* 1997; **277**: 528–9 (Book review).
2 Van de Watering LMG, Houbiers JGA, Hermans J *et al.* Leukocyte depletion reduces postoperative mortality in patients undergoing cardiac surgery. *Br J Haematol* 1996; **93**: 312 (Abstract).
3 Van de Watering LMG, Hermans J, Houbiers JGA *et al.* Beneficial effects of leukocyte depletion of transfused blood on postoperative complications in patients undergoing cardiac surgery. *Circulation* 1998; **97**: 562–8.
4 Jensen LS, Andersen AJ, Christiansen PM *et al.* Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. *Br J Surg* 1992; **79**: 513–16.
5 Jensen LS, Kissmeyer-Nielsen P, Wolff B, Qvist N. Randomised comparison of leucocyte-depleted *versus* buffy-coat-poor blood transfusion and complications after colorectal surgery. *Lancet* 1996; **348**: 841–5.
6 Busch ORC, Hop WCJ, Hoynck van Papendrecht MAW, Marquet RL, Jeekel J. Blood transfusions and prognosis in colorectal cancer. *N Engl J Med* 1993; **328**: 1372–6.
7 Heiss MM, Mempel W, Jauch K-W *et al.* Beneficial effects of autologous blood transfusion on infectious complications after colorectal cancer surgery. *Lancet* 1993; **342**: 1328–33.
8 Houbiers JGA, Brand A, Van de Watering LMG *et al.* Randomised controlled trial comparing transfusion of leuco-

cyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer. *Lancet* 1994; **344**: 573–8.
9 Heiss MM, Fasolmerten K, Allgayer H *et al.* Influence of autologous blood transfusion on natural killer and lymphokine-activated killer cell activities in cancer surgery. *Vox Sang* 1997; **73**: 237–45.

Author's reply

Sir

We followed closely the recommended protocols of the Cochrane Collaboration[1] and the NHS Centre for Reviews and Dissemination[2] in conducting this meta-analysis and, therefore, refute Dr Jensen's claim that we lacked scientific objectivity or used inappropriate methodology.

In addition to the pitfalls of meta-analysis mentioned by Dr Blumberg, another common mistake is the attempt to combine studies with widely disparate patients, protocols and outcomes to obtain a summary risk ratio. Such an analysis, which neglects between-trial heterogeneity, is clearly inappropriate[3]. One of the key aspects in the conduct of any meta-analysis is to start with a focused question, in our case whether transfusion of allogeneic blood to patients with cancer increases mortality, cancer recurrence and postoperative infection rates. As the clinic to which Dr Blumberg refers enrolled patients without cancer and did not assess outcomes we were interested in, it was excluded from the analysis although referenced.

Dr Jensen questions the use of the Jadad scale to grade the quality of the six identified randomized trials, pointing out that Blajchman[4] (in an editorial, not a meta-analysis) categorized five of the studies as level 1 studies. Level 1 evidence simply refers to evidence derived from randomized clinical trials but at no point does Blajchman discuss the methodological quality of each trial. Indeed, 'the assumption that all randomized clinical trials with a common content area are of equal quality may be erroneous'[3]. The Jadad scale is commonly used to evaluate the methodological rigour of clinical trials and was systematically developed using standard scale development techniques[5]. We felt that use of this scale was the most objective means by which to grade the quality of the included trials.

Dr Jensen seems to suggest that our findings are at odds with those expressed by Blajchman in his editorial, but Blajchman states clearly that there are 'contradictory data from the six available level 1 studies' and calls for a pooling of data from each investigator for an individual-patient data meta-analysis to determine 'whether or not allogeneic blood transfusions are associated with an increased risk of postoperative infection'[4]. I believe this conclusion is concordant with our statements that there is 'a paucity of evidence underlying claims about the hazardous effects of perioperative allogeneic blood transfusion' and that 'more studies are required before a definitive statement can be made'.

Dr Jensen asserts that all of the identified studies separately demonstrated significantly increased rates of infectious complications in transfused *versus* non-transfused patients. This comparison does not contribute to the question at hand (and the focus of our meta-analysis). Confounding conditions that are associated with both an increased likelihood of transfusion and a worse prognosis have to be taken into account. It would be incorrect to compare event rates in transfused patients to those in non-transfused patients. In the absence of trials randomizing patients to allogeneic transfusion or no transfusion, I believe the use of clinical trials that randomized patients to allogeneic transfusion or active controls (autologous or leucocyte-depleted allogeneic blood) was the only acceptable alternative. While Dr Jensen believes that we 'confused transfused and non-transfused patients', we did use the intention-to-treat principle in assigning outcomes, which is a standard approach to the analysis and interpretation of clinical trials.

Dr Blumberg suggests that we were able to obtain a statistically non-significant risk ratio only by excluding Dr Jensen's trials but the summary risk ratios (*Table 4* and *Fig. 1* of our paper) included all six trials. While Dr Jensen points to the summary risk ratio of 1·63 for postoperative infections as evidence that there is an increased risk with allogeneic transfusion, he neglects the 95 per cent confidence intervals in *Table 4*. Even when his two trials are included, the 95 per cent confidence interval for the summary risk ratio crosses one (implying that any observed difference in event rates between allogeneic and control patients was not statistically significant). The small sample sizes of these six studies mean that the available evidence is insufficient to rule out a relative increase in postoperative infection of 10 per cent (or less) from allogeneic blood. The limitations of meta-analyses with small sample sizes tend to overestimate treatment effects and we believe our conclusions are valid.

Although Dr Jensen feels we made 'major criticisms of the excluded studies', we merely pointed out possible sources of the statistical heterogeneity in the postoperative infection data. As heterogeneity refers to differences between trials, I am puzzled by the argument that the identified differences between trials do not fulfil 'criteria for heterogeneity'.

Finally, while Dr Blumberg identifies several potential sources of information on causality, we focused our attention on the highest level of evidence: the randomized controlled trial. While the other sources of information are useful in generating hypotheses, medicine is replete with examples of therapies that appeared very beneficial from epidemiological evidence, animal studies or mechanistic studies, but did not provide clinical benefits when subjected to rigorous testing in clinical trials.

Our meta-analysis was rigorously and objectively conducted, summarized the totality of the published evidence, and highlighted the paucity of evidence underlying claims of adverse sequelae from the use of allogeneic blood products.

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5 Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Controlled Clin Trials* 1995; **16**: 62–73.

Book reviews

Stents in Endovascular Surgery: Basic Concepts and Techniques

F. J. Criado (ed.). 278 × 215 mm. Pp. 124. Illustrated. 1996. Armonk, New York: Futura Publishing. $49.

This 120-page glossy book describes in 16 chapters some of the basic concepts involved in the placement of metallic endovascular stents throughout the vascular system: to its credit, many of the pictures are very pretty. However, there is much to be questioned in the text. The author has some interesting thoughts on training in endovascular techniques. He chooses to contradict the published guidelines from his own country and considers it unnecessary for trained vascular surgeons to embark on a full 1-year 'endovascular fellowship'. He goes on to state that 'whether surgeons only participate or are the primary operators is not critical, as long as the experience is certified', and that a knowledge of thrombolysis alone is sufficient for initial credentialling – personal experience is not critical. All this is to ensure 'the surgeon's continued pre-eminence in the treatment of vascular disease'. Sadly, these political thoughts are about as relevant to the UK as the remainder of the text. The book almost exclusively focuses on the use of the Palmaz stent, a shame as this will soon only be available in museums. Clinical indications with outcome data are strictly avoided, and there are many practices peculiar to the author's own experience. Subintimal recanalization is considered undesirable, he suggests a brachial arteriotomy for subclavian stenoses, dextran is used routinely, modern contrast agents are only to be used selectively, and stents are to be deployed in almost every case of iliac angioplasty. There are many well written, well referenced textbooks on the endovascular management of vascular disease. This is not one of them

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The Pathophysiology of Pneumo-peritoneum

R. J. Rosenthal, R. L. Friedman and E. H. Phillips (eds). 240 × 158 mm. Pp. 187. Illustrated. 1998. Heidelberg: Springer. £57.

Laparoscopy and laparoscopic surgery have become frequent surgical procedures. Of necessity, laparoscopy requires pneumoperitoneum. The majority of technically related complications to laparoscopic surgery are caused by the establishment and maintenance of pneumoperitoneum. The very significant impact of this on respiration and blood flow to central and peripheral organs has not been given very much attention among surgeons. This multiauthor book provides a detailed overview of the physiological changes that are induced by pneumoperitoneum and their pathogenesis. In addition to the influence of various gases, their temperatures and the technical details of establishing pneumoperitoneum, the cardiovascular and respiratory influences are reviewed. Each chapter has a detailed reference list including clinical as well as experimental papers published in 1996 and earlier. With the frequency of laparoscopic procedures we see today it is a necessity for surgeons to be aware of and understand these pathophysiological changes. This 180-page book provides the data needed and it therefore fills a gap in the market. It will allow updating of knowledge and it should serve as a reference volume in the department library.

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Ductal Carcinoma *in situ* of the Breast

M. J. Silverstein (ed.). 283 × 220 mm. Pp. 665. Illustrated. 1997. Baltimore, Maryland: Williams and Wilkins. £115.

Ductal carcinoma *in situ* of the breast (DCIS) was a rare disease before 1980, representing less than 1 per cent of all breast cancers. With the improvement in the technique of mammography and its use as a screening tool in asymptomatic women, the diagnosis is now made more frequently. At the present time, DCIS represents 15 per cent of all new breast cancers diagnosed. It is a controversial topic. There are those who argue that DCIS only rarely develops into invasive cancer, and so looking for it and treating it represents overdiagnosis. On the other hand, there are those who argue that lives can be prolonged by actively seeking it out and extirpating it.

This book is the first to gather together all the information currently available about DCIS. It attempts to be comprehensive and, despite the rapidly increasing knowledge about DCIS, is largely successful. It deals with the biology and pathology of the condition, as well as its diagnosis and treatment, bringing together the competing views of those who favour a total mastectomy and those who use minimal treatment. The evidence derived from randomized clinical trials and other evidence is 'overviewed'; much of this evidence comes from British and European sources. It also deals with the psychosocial aspects, including chapters by those with a wide experience of helping women who are well, have a mammogram, and suddenly have cancer. There are chapters by women who have suffered this sort of event so that the reader learns what it is like from the inside. I learned a great deal from this book, and will go on doing so. I shall keep it on my bookshelf so that I may go back to it on many occasions to check facts and ascertain what others have done in a particular situation. I am sure it will be a useful reference book for those who are not breast cancer surgeons, and it is an important book which must be available for consultation in every medical library.

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Scientific Surgery

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Randomized trials

Valentine RJ, Duke ML, Inman MH, Grayburn PA, Hagino RT, Kakish RT *et al.* Effectiveness of pulmonary artery catheters in aortic surgery: a randomized trial.
J Vasc Surg 1998; **27**: 203–12.
The authors studied 120 patients but were not able to show any advantage for routine use of pulmonary artery catheters.

AbuRhama AF, Robinson PA, Saiedy S, Khan JH, Boland JP. Prospective randomized trial of carotid endarterectomy with primary closure and patch angioplasty with saphenous vein, jugular vein and polytetrafluoroethylene: long term follow up.
J Vasc Surg 1998; **27**: 222–34.
Some 399 operations were included; both patches were associated with a reduced perioperative stroke rate, and also reduced late restenosis, especially in women.

Cascinelli N, Morabito A, Santinami M, MacKie RM, Belli F on behalf of the WHO Melanoma Programme. Immediate or delayed dissection of regional nodes in patients with melanoma of the trunk: a randomised trial.
Lancet 1998; **351**: 793–6.
In a multicentre study of 252 patients, immediate node dissection improved 5-year survival from 27 to 48 per cent in patients who had involved nodes but did not affect outcome if the nodes were clear.

Kiviluoto T, Siren J, Luukkonen P, Kivilaasko E. Randomised trial of laparoscopic *versus* open cholecystectomy for acute and gangrenous cholecystitis.
Lancet 1998; **351**: 321–5.
Sixty-three patients were randomized. In the hands of these experts, laparoscopic cholecystectomy resulted in fewer complications and a shorter hospital stay.

Hosch SB, Knoefel WT, Pichlmeier U, Schulze V, Busch C, Gawad KA *et al.* Surgical treatment of piles. Prospective, randomized study of Parks *vs.* Milligan-Morgan hemorrhoidectomy.
Dis Colon Rectum 1998; **41**: 159–64.
Postoperative pain, duration of hospital stay and time to return to work were all less after Parks' operation in this study of 34 patients.

MacRae HM, McLeod RS. Handsewn *vs.* stapled anastomoses in colon and rectal surgery. A meta-analysis.
Dis Colon Rectum 1998; **41**: 180–9.
This review included 13 randomized trials and concluded that there is little clinical difference between the two techniques.

Merad F, Hay J-M, Fingerhut A, Flamant Y, Molkhou J-M, Laborde Y. Omentoplasty in the prevention of anastomotic leakage after colonic or rectal resection: a prospective randomized trial in 712 patients.
Ann Surg 1998; **227**: 179–86.
In this multicentre trial, omentoplasty did not reduce the frequency or severity of anastomotic leakage.

Morlian BJ, Stehle P, Wachtler P, Siedhoff H-P, Koller M, Konig W *et al.* Total parenteral nutrition with glutamine dipeptide after major abdominal surgery. A randomized, double-blind, controlled study.
Ann Surg 1998; **227**: 302–8.
In the 28 patients evaluated, glutamine enriched TPN improved nitrogen balance and lymphocyte recovery, and shortened hospital stay

Lai ECS, Lo C-M, Fan S-T, Liu C-L, Wong J. Postoperative adjuvant chemotherapy after curative resection of hepatocellular carcinoma: a randomized controlled trial.
Arch Surg 1998; **133**: 183–8.
Sixty-six patients were included; the regimen of intravenous epirubicin and transarterial cisplatin actually reduced survival.

Rogers DA, Hatley RM, Howell CG Jr. A prospective, randomized comparison of traditional and laparoscopic inguinal exploration in children.
Am Surg 1998; **64**: 119–21.
In this pilot study of 18 children, there were no complications and the duration of surgery was similar for each method.

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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On the title page give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone, facsimile and e-mail numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, review etc.).

Abstract

This should be not more than 200 words on the second page of the manuscript and be presented in a structured format. **Background:** state why the study was done, and its main aim; **Method:** describe patients, laboratory material and other methods used. Clearly identify the nature of the study: randomized controlled trial, retrospective review, experimental study, etc. **Results:** state the main findings of the study; include important numerical values. **Conclusion:** state the main conclusion drawn from the results. Controversial or unexpected observations may be highlighted, but keep this section brief. Write the abstract in clear prose.

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Use abbreviations sparingly. Terms that are mentioned frequently may be abbreviated but only if this does not impair comprehension by the reader. Use abbreviations consistently throughout the text and clearly define each one on first use.

Numbers and units

Use the decimal point, not a comma, e.g. 5·7. Use a space and not a comma after thousands and multiples thereof, e.g. 10 000. Use SI units (International System of Units) except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, give the actual values and units, with SI equivalents inserted in parentheses at appropriate points.

Statistics

For detailed guidance on the handling of statistical material, consult *Br J Surg* 1991; **78**: 782–4. In evaluating a manuscript the Editors and statistical referees will consider the design of the study, the presentation and analysis of data and the interpretation of results.

Design

Set out clearly the objectives of the study, identify the primary and secondary hypotheses, and the chosen end-points, and explain the rationale for the choice of sample size. Investigators embarking on randomized controlled studies may wish to consider the CONSORT statement (*JAMA* 1996; **276**: 637–9).

Presentation

Whenever possible use graphical presentation to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. Do not use the '±' symbol; these statistics should be presented in parentheses after the mean value.

Analysis

Clearly describe which methods were used for which analyses; any methods not in common usage should be supported by references. Report results of statistical tests by stating the value of the test statistic, the number of degrees of freedom and the *P* value, e.g. '*t* = 1·34, 16 d.f., *P* = 0·20'.

Actual *P* values should be reported to two decimal places, especially when the result is not significant, rather than stating 'not significant'. Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Do not confuse statistical significance with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Beware of placing undue emphasis on secondary analyses, especially when they are suggested by an inspection of the data.

References

Type the references with double spacing in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged. Reference to unpublished communications will not be accepted. Cite personal communications in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, number the references consecutively by superscript: ^{1} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation is quoted); year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66**: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer, 1981: 123–63.